IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

VIIV HEALTHCARE UK LTD. AND VIIV HEALTHCARE CO.,	:	
Plaintiffs,	:	
v.	:	C.A. 11-576-RGA (CONSOLIDATED)
LUPIN LTD. AND LUPIN PHARMACEUTICALS, INC., TEVA PHARMACEUTICALS, INC.,	:	
Defendants.	:	

TRIAL OPINION

Brian E. Farnan, Esq., Wilmington, Delaware; F. Christopher Mizzo, Esq., Washington, D.C.; Gregg F. LoCascio, Esq., Washington, D.C.; Charles A. Fernandez, Esq., Washington, D.C.; Tiffany P. Cunningham, Esq., Chicago Illinois; Craig T. Murray, Esq., Washington, D.C.; Attorneys for Plaintiffs ViiV Healthcare UK Limited and ViiV Healthcare Co.

John C. Phillips, Jr., Esq., Wilmington, Delaware; Deanne M. Mazzochi, Esq., Chicago, Illinois.; Paul J. Molino, Esq., Chicago, Illinois; Neil A. Benchell, Esq., Chicago, Illinois; Rachel P. Waldron, Chicago, Illinois; Matthew T. Lord, Esq., Chicago, Illinois; Attorneys for Defendants Lupin Ltd. and Lupin Pharmaceuticals, Inc.

Richard L. Horwitz, Esq., Wilmington, Delaware; Ira J. Levy, Esq., New York, New York; Annemarie Hassett, Esq., New York, New York; Gregory T. Sandidge, Esq., New York, New York; Attorneys for Defendant Teva Pharmaceuticals USA, Inc.

December 17 2013
Wilmington, Delaware

ANDREWS, UNITED STATES DISTRICT JUDGE:

Plaintiffs ViiV Healthcare UK Ltd. and ViiV Healthcare Co. (collectively "ViiV") assert U.S. Patent No. 6,417,191 ("the `191 Patent") against Defendants Teva Pharmaceuticals, Inc. ("Teva"), Lupin Ltd., and Lupin Pharmaceuticals, Inc. (collectively "Lupin"). The `191 Patent (JX 1) is titled "Synergistic Combinations of Zidovudine, 1592U89 and 3TC." [1](D.I.178, Ex. 1 ¶ 7). The patent issued on July 9, 2002, and expires on March 28, 2016. (*Id.* ¶¶ 7, 9). The named inventors are David Walter Barry and Martha Heider St. Clair. *Id.* ¶ 8. The patent claims recite formulations and methods of treating HIV infection, using (a) the "triple combination" of abacavir, zidovudine, and 3TC; or (b) the "double combination" of abacavir and 3TC. (JX 1 cols. 12-16).

ViiV holds NDA No. 21-205 for Trizivir, an oral tablet dosage form, which the FDA approved in November 2000 as an HIV drug. (D.I. 178, Ex. 1 ¶¶ 13-15). Trizivir contains the "triple combination" of abacavir, 3TC, and AZT. ViiV also holds NDA No. 21-652 for an oral tablet dosage form for Epzicom, which the FDA approved in August 2004 as an HIV drug. (*Id.* ¶ 20). Epzicom contains the "double combination" of abacavir and 3TC. The FDA's Orange Book lists ViiV's `191 Patent in connection with both products. (*Id.* ¶¶ 16, 23). ViiV's case against Teva and Lupin arises out the Defendants' ANDA filings with the FDA. Teva seeks FDA approval to market a generic version of Epzicom, while Lupin seeks FDA approval for a generic version of Trizivir. (*Id.* ¶ 17).

Defendants assert that the `191 Patent is invalid as obvious. Lupin individually asserts that the `191 Patent is invalid due to lack of enablement and utility, and also asserts that its proposed generic product does not infringe the `191 Patent. The Court held a four and a half day

[1] Zidovudine is also referred to as "AZT." "1592U89" is also referred to as "abacavir" or "ABC." "3TC" is also referred to as "lamivudine." The terms are used interchangeably throughout the opinion.

bench trial on June 24, 25, 26, 27, and 28.[2] Defendants failed to prove any of their invalidity defenses by clear and convincing evidence, while ViiV failed to prove that Lupin's generic drug product infringes the asserted claims of the `191 Patent.

I. INFRINGEMENT

ViiV asserts that Lupin's generic product would infringe claims 4, 26, 27, 29, 30, 34, 36, 38, 39, and 47 of the `191 Patent. Claim 47 is a formulation claim, while the remaining claims recite methods of treatment. All claims encompass abacavir and 3TC, while certain claims add AZT as the third drug in the combination. There is no dispute that Lupin's ANDA product will contain AZT and 3TC. The infringement dispute hinges on the abacavir limitation, and whether Lupin's ANDA product's use of abacavir sulfate puts the product outside the scope of the asserted claims. Lupin argues that it does not infringe any of the claims because (1) the asserted claims do not encompass the sulfate form of abacavir; (2) the method claims are only directed to treating the "opportunistic conditions" associated with HIV rather than the HIV infection itself; and (3) there is no evidence that Lupin would induce and contribute to the infringement of the method claims. ViiV disagrees, arguing that (1) abacavir is contained by the abacavir sulfate in Lupin's generic product; (2) the method claims are aimed at the treatment of the underlying HIV infection; and (3) Lupin clearly intends to infringe the method claims by inducing and contributing to use by clinicians and patients of the claimed combinations.

(A) FINDINGS OF FACT

1. Independent claim 45 recites the chemical compounds of AZT, 3TC, and pure abacavir, also referred to as abacavir free base. `191 Patent, claim 45.

2. Claim 46 depends from claim 45, reciting the formulation of claim 45 in a unit dosage form. `191 Patent, claim 46.

[2] (Transcripts available at D.I. 192, 193, 194, 195, and 196).

3. Claim 47 depends from claim 46, reciting the formulation of claim 46 in the form of a tablet capsule. `191 Patent, claim 47.

4. Claim 47 is asserted against Lupin.

5. Lupin's proposed ANDA product contains abacavir sulfate, also referred to as the salt form of abacavir, 3TC, and AZT. (*See, e.g.*, PTX 135 at 1; PTX 136 at 15; PTX 137 at 44).

6. Abacavir sulfate is formed via a chemical reaction between abacavir free base and sulfuric acid. (Tr. at 215-17, 228, Dr. Langer).

7. Abacavir sulfate has different molecular bonds and a different molecular weight from free base abacavir. (Tr. at 215-17, 228, Dr. Langer).

8. Abacavir sulfate is a distinct chemical compound from free base abacavir. (Tr. at 254-56, Dr. Arnold).

9. The `191 Patent does not define claim 47 to encompass abacavir sulfate, and thus Lupin's generic product does not literally infringe claim 47.

10. There is no evidence that abacavir sulfate and free base abacavir are functional equivalents, as abacavir sulfate has superior stability and handling properties. (Tr. at 220, Dr. Langer; Tr. at 254-55, Dr. Arnold).

11. Claims 4, 26, 27, 29, 30, 34, 36, 38, and 39 of the `191 Patent encompass treatment of the underlying HIV infection rather than merely treatment of the opportunistic infections associated with AIDS. `191 Col. 1:09-20.

12. Claim 4 does not encompass any "physiologically functional derivative" of abacavir, and thus Lupin's generic product does not literally infringe that claim. *See* `191 Patent, claim 1-4.

13. Claims 26, 27, 29, 30, 34, 36, 38, and 39 do not encompass the salt form of abacavir, and thus Lupin's generic product does not literally infringe those claims. *See* `191 Patent, claims 26, 27, 29, 30, 34, 36, 38, and 39.

14. Lupin's generic product does not infringe claims 4, 26, 27, 29, 30, 34, 36, 38, and 39 under the doctrine of equivalents.

(B) LEGAL DISCUSSION AND CONCLUSIONS OF LAW

(i) Literal infringement of claim 47

ViiV first argues that Lupin's generic product will directly infringe claim 47 of the '191 Patent, which is a formulation claim. ViiV has the burden to prove infringement by a preponderance of the evidence. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 438 F.3d 1354, 1363 (Fed. Cir. 2006). Claim 47 depends from claim 46, which depends from claim 45. Those three claims follow:

> 45. A pharmaceutical formulation comprising (1S, 4R)-cis-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol, zidovudine, and (2R, cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one in a ratio of 1 to 20:1 to 20:1 to 10 by weight, in association with one or more pharmaceutically acceptable carriers therefor.
>
> 46. A formulation according to claim 45 in a unit dosage form.
>
> 47. A formulation according to claim 46 in the form of a tablet capsule.

ViiV asserts that independent claim 45 recites abacavir, AZT, and 3TC, and Lupin's generic tablet capsule product will infringe dependent claim 47, which claims a tablet capsule unit dosage form. In support, ViiV points to Lupin's ANDA, which states that Lupin's generic drug product will contain abacavir, AZT, and 3TC as the active ingredients. In response, Lupin argues that claim 47 is limited to the chemical formulation of "abacavir free base," *i.e.*, pure abacavir. Lupin argues that its generic product does not contain "abacavir free base," but rather uses "abacavir sulfate," or a salt form of abacavir. According to Lupin, the salt form of abacavir has a chemical structure that differs from pure abacavir, and the salt form's chemical structure is not encompassed by claim 47. ViiV replies that this is a distinction without a difference, as abacavir sulfate invariably contains abacavir.

ViiV is correct when it says that Lupin's ANDA, in certain places, explicitly states that abacavir, AZT, and 3TC are the ingredients of the generic product. (*See, e.g.*, PTX 152 at LUPIN(TRIZ) 012340; *id.* at 012373). Lupin's 30(b)(6) witnesses also stated as much: "Our

product is abacavir, lamivudine and zidovudine tablets."[3] (Tr. at 150-151, Mr. Dahibate). Dr. Langer, ViiV's expert on infringement, further testified that "abacavir is in abacavir sulfate...Lupin's ANDA says that." (Tr. at 189). Lupin's ANDA further states that "each film-coated tablet contains the active ingredients 300 mg of abacavir as abacavir sulfate." (PTX 154 at LUPIN(TRIZ) 000102). Dr. Arnold, Lupin's expert, acknowledged that Lupin's product "eventually provides abacavir. That is the active ingredient. Otherwise, the product wouldn't work." (Tr. 280).

These statements in isolation would suggest that Lupin's proposed generic drug contains the identical chemical compound recited in independent claim 45 and is thus encompassed by asserted dependent claim 47. The sum total of the evidence, however, shows otherwise. Lupin's ANDA product will use abacavir in a salt form, i.e., abacavir sulfate, not abacavir in its free base or pure form. Each ANDA section proffered by ViiV identifies the active ingredient as "abacavir sulfate." (*See, e.g.*, PTX 135 at 1; PTX 136 at 15; PTX 137 at 44). The proposed ANDA labeling expressly defines the active ingredient as the sulfate or salt form. (PTX 152 at 12355). Although ViiV argues that abacavir is "in" abacavir sulfate, the sulfate form comes into being only after a reaction between abacavir free base and sulfuric acid in isopropyl alcohol, and the resulting salt product has a changed molecular weight and forms new molecular bonds. (Tr. at 215-17, 228, Dr. Langer). As the salt form is only produced after a chemical reaction, it is chemically distinct from abacavir free base or pure abacavir. (Tr. at 254-56, Dr. Arnold). It thus does not contain abacavir free base as recited in claim 45. As to the 30(b)(6) testimony, Mr. Dahibate also testified to the cover letter for the ANDA, which recites abacavir sulfate, lamivudine, and zidovudine tablets. (Tr. at 152-53). There is no question that Lupin's proposed

[3] *See also* tr. at 164, Mr. Raghavan ("Yes. [Lupin's generic product] provides lamivudine, zidovudine and abacavir.")).

tablet must use the sulfate form of abacavir, and not abacavir free base, if it is to be consistent with the ANDA submitted to the FDA. (*See* PTX 152 at 5) (generic drug contains "300 mg of abacavir as abacavir sulfate"). A 30(b)(6) witness's testimony does not alter the directions provided in the ANDA document, and any generic product must be consistent with the content of the relevant ANDA.

ViiV argues that Lupin's planned use of abacavir sulfate in combination with AZT and 3TC nevertheless infringes claim 47, as the tablet capsule eventually provides abacavir when it is administered to a patient. ViiV relies on *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 347 F.3d 1367, 1371 (Fed. Cir. 2003) to argue that even if the sulfate form is chemically distinct from abacavir free-base, claim 45 would be understood by a person skilled in the art as encompassing the salt form. In *Merck & Co.*, the Federal Circuit upheld the district court's finding that the salt form of an acid drug compound infringed the sole claim of the patent, which was a method claim, even though that claim recited only the acid form and not the salt form. *Id.* at 1372. The Federal Circuit stated the following:

> The evidence of all the qualified witnesses was that persons in this field would understand that the acid is the active agent and that the acid is administered when it is in the form of the salt. There was no evidence that the claimed method of treatment is not achieved by the acid salt. The record shows that Teva and Zenith, as well as Merck, label their products with the "free acid equivalent."

Id. at 1371. The chemical distinction between an acid and a salt was thus discounted, as pharmacologists skilled in the art would have understood the claimed method of treatment to encompass the salt. *Id.* at 1371-72. ViiV argues that similarly, the Court should conclude that the sulfate of abacavir falls within the scope of abacavir in the free base form. In support, ViiV points to the specification's statement that "therapeutic use" included "salts of [abacavir]," and that "all salts, whether or not derived from a physically acceptable acid or base, are within the

scope of the present invention." `191 Col. 3:25-27. ViiV also directs attention to dependent claim 35, which states the following: "a method according to claim 32, wherein the [abacavir] is the succinate salt," suggesting that the abacavir chemical is intended to include the salt form.

Lupin argues that *Merck & Co.* is not on point. First, Lupin notes that the claim at issue in that case recited methods of treatment, whereas claim 47 is a chemical formulation claim. Lupin argues that because it was a method claim in *Merck & Co.*, rather than a formulation claim, the district court was able to apply a special lexicography to define the acid compound as including salts, as the district court relied on the "biology" section of that patent's specification that was more relevant to the method of treatment, while ignoring the "chemical" section. *Merck & Co. v. Teva Pharms. USA, Inc.*, 228 F. Supp. 2d 480, 489 (D. Del. 2002). Lupin argues that the district court noted that this was only proper because a method claim was at issue, and the district court would not have done so if the claim "were still a composition claim," since, in that context, the chemistry section "would be highly instructive." *Id.* The Federal Circuit's affirmation of the district court's opinion was similarly dependent on the claim's form as a method claim. *See Merck & Co.*, 347 F.3d at 1372. Further, Lupin argues that construing the only claim of the patent at issue in *Merck & Co.* as excluding the salt form would have rendered salt form embodiments described in the specification completely excluded from the patent. Here, in contrast, there are unasserted claims specifically directed at "physiological functional derivatives," meaning that the salt embodiments described in the `191 Patent would not be excluded by Lupin's construction, and also suggesting that when the inventors intended to claim derivatives, they did so explicitly, and thus the derivatives should not be read as encompassed by the method claims.

The Court agrees with Lupin that the present facts are distinguishable from *Merck & Co.*

Merck & Co. dealt with a method claim that recited a "method of treatment" that "consists of administering to a patient in need thereof an effective amount of [the drug compound]." *Id.* at 1370. The Federal Circuit relied on the fact that "[t]he evidence of all the qualified witnesses was that persons in this field would understand that the acid is the active agent and that the acid is administered when it is in the form of the salt." *Id.* at 1371. The claim in that case encompassed therapeutic treatments, and there were multiple statements in the specification suggesting that the method of treatment included the salt form. Claim 47 is not a method claim reciting the administration of a drug to a patient for a certain therapy. It is solely a formulation claim, unconcerned with the ultimate effects of the drug compound in the body. Further, there are unasserted claims of the `191 Patent explicitly reciting "physiological functional derivatives" of the drugs, which would include the salt form. Thus, the patentee differentiated between the pure (or free base) form of abacavir and the salt form in the claims themselves, undermining the argument that the salt form is intrinsically encompassed by the free base or pure form. The Court's ruling does not exclude salt forms altogether from the scope of the patent, as there are unasserted claims that encompass derivatives. If salts and derivatives of abacavir were intended to be encompassed by the chemical compound as recited, then there would have been no need for the patentee to claim derivatives and salts of abacavir separately.

As to ViiV's claim differentiation argument, ViiV correctly states that claim 35 narrows the "1S-methanol" [abacavir] element of claim 32 to "the succinate salt." As Lupin notes, however, the inventors were inconsistent in their use of dependent claims. Claim 32 claims in part "1S-Methanol" [abacavir]. It does not claim a physiologically functional derivative thereof. Claim 35 depends from claim 32, and narrows the claim to where the "1S-Methanol" [abacavir] is the "succinate salt," implying that the "succinate salt" is claimed by "1S-methanol" [abacavir].

Claim 48 recites the "1S-methanol" [abacavir] element with "or a physiologically functional derivative thereof." Then, dependent claim 49 narrows claim 48 to where the "physiologically functional derivative of '1S-Methanol' [Abacavir]" is the "succinate salt." In one case, the succinate salt is a limitation on "1S-methanol" [abacavir] and the other time it is a limitation on the derivative of "1S-methanol" [abacavir]. The patentee excludes the "1S-methanol" limitation, instead only reciting the "derivative" limitation narrowed to the "succinate salt." The "succinate salt" claims are inconsistent. The patentee cannot benefit from inconsistent claims drafting.[4]

For these reasons, the Lupin generic ANDA product does not literally infringe claim 47 of the `191 Patent.

(ii) Infringement of claim 47 under doctrine of equivalents

ViiV next argues that Lupin's generic ANDA product infringes under the doctrine of equivalents. The primary inquiry in applying the doctrine of equivalents is whether "the differences between the claimed invention and the accused device are . . . 'insubstantial.'" *nCUBE Corp. v. SeaChange Int'l, Inc.*, 313 F. Supp. 2d 361, 376 (D. Del. 2004), *aff'd,* 436 F.3d 1317 (Fed. Cir. 2006). A salt form of a drug has properties distinct from the pure or free base form, as the entire purpose behind using the salt form is the form's superior stability and handling properties. (Tr. at 220, Dr. Langer; Tr. at 254-55, Dr. Arnold). This suggests that the salt and the free base forms are not equivalent, and no evidence was provided otherwise. Further, as discussed, there are unasserted claims that explicitly recite "physiologically functional derivatives" of abacavir. ViiV chose not to assert those claims against Lupin, instead asserting a claim that does not contain that limitation. It would be improper to recapture scope

[4] As Lupin notes, (D.I. 210 at 12), the claims drafting belies that any particular care went into it. For example, claim 40 is a duplicate of claim 35.

that is absent in the asserted claim, yet present in unasserted claims, under the doctrine of equivalents. *See Abbott Laboratories v. Sandoz, Inc.*, 566 F.3d 1282, 1297 (Fed. Cir. 2009).

(iii) Literal infringement of method claims 4, 26, 27, 29, 30, 34, 36, 38, and 39

ViiV also asserts method claims 4, 26, 27, 29, 30, 34, 36, 38, and 39 of the `191 Patent, all reciting methods "for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises treating said animal with a therapeutically effective amount of" a combination of abacavir, 3TC, and optionally AZT. ViiV asserts theories of indirect infringement, arguing that Lupin's ANDA shows it would induce and/or contribute to acts of direct infringement of the method claims by doctors and patients.

To induce infringement, the defendant must intend to cause the acts that constitute the direct infringement, *DSU Medical Corp. v. JMS Co.*, 471 F.3d 1293, 1305 (Fed. Cir. 2006), and must know that the induced acts constitute infringement. *Global-Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068-71 (2011). To be held liable for contributory infringement, ViiV must show that Lupin will sell its generic product knowing that it will be used in an infringing manner. *Netgear, Inc. v. Ruckus Wireless, Inc.*, 852 F. Supp. 2d 470, 476 (D. Del. 2012). Claims 34, 35, 38, and 39 are nearly identical to claims 26, 27, 29, and 30, except that claims 26, 27, 29, and 30 recite methods of treatment using a combination "comprising" ABC and 3TC, thus permitting (but not requiring) AZT. Those claims are recited below:

Double combination claims (26, 27, 29, 30)	Triple Combination Claim (34, 36, 38, 39)
20. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises treating said animal with a therapeutically effective amount of a	**32.** A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises treating said animal with a therapeutically effective amount of a

combination comprising [abacavir] and [3TC].	combination comprising [abacavir], zidovudine, and [3TC]
26. A method according to claim **20** wherein each [abacavir] and [3TC] is present in an amount from 5 to 1000 mg per unit dosage form.	**34.** A method according to claim **32** wherein each [abacavir], zidovudine, and [3TC] is present in an amount from 5 to 1000 mg per unit dosage form.
27. A method according to claim **20** wherein the combination is administered simultaneously.	**36.** A method according to claim **32** wherein the combination is administered simultaneously.
29. A method according to claim **20** wherein the combination is administered as a single combined formulation.	**38.** A method according to claim **32** wherein the combination is administered as a single combined formulation.
30. A method according to claim **20** in which said animal is a human.	**39.** A method according to claim **32** in which said animal is a human.

All of the asserted method claims (or the independent claims from which they derive) recite the following limitation: "the treatment or prevention of the symptoms or effects of an HIV infection." The parties dispute whether treatment or prevention of the HIV infection itself falls within the scope of "symptoms or effects." Lupin argues that the plain meaning of "symptoms or effects" of HIV is limited to opportunistic infections or conditions and not to the HIV infection itself. Because its generic drug product is intended to treat HIV infection, not the symptoms or effects of an infection, Lupin argues it does not indirectly infringe the claims. ViiV disagrees, arguing that Lupin's generic product is aimed at halting replication of HIV, which is an effect of infection, and it therefore infringes that limitation. The Court construed the "symptoms or effects" term according to its plain and ordinary meaning, but did not specify what this plain and ordinary meaning was, or whether that meaning excluded treatment of the HIV infection itself. (D.I. 126 at 2, 3).

Lupin argues that construing "symptoms or effects" to include the HIV infection itself would simply remove the term from the claim in the following manner:

> **32.** A method for the treatment or prevention ~~of the symptoms or effects~~ of an HIV infection in an infected animal. . . .

The Court does not agree. The `191 Patent is aimed at treatments designed to halt viral replication. (Tr. at 81-82, Dr. Blick). The first paragraph of substance in the specification states, "The present invention relates to therapeutic combinations of [the drug compounds] which have anti-HIV activity. The present invention is also concerned with pharmaceutical compositions containing said combinations and their use in the treatment of HIV infections including infections with HIV mutants bearing resistance to nucleoside and/or non-nucleoside inhibitors." `191 Col. 1:09-20. The specification makes clear that the combinations are designed to treat an HIV infection by inhibiting replication of the HIV virus. There is nothing wrong with construing the "symptoms or effects" claim language to encompass such treatment, especially when those terms are read in light of the specification. "Symptoms" and "effects" are not equivalent. While "symptoms" might be understood to have the restrictive scope argued by Lupin, "effects" is a broader term. One "effect" of an HIV infection is the nonstop viral replication resulting in a spread of infection throughout the cells of the body. There is no dispute that Lupin's ANDA product is intended to halt such progression of the disease. (*See* PTX 152 at LUPIN(TRIZ) 12337). It is thus a method for the treatment of the effects of an HIV infection.

The claim language also concerns the "prevention" of symptoms of an HIV infection. One way to prevent the opportunistic conditions (which Lupin argues is what is meant by "symptoms or effects of an HIV infection") associated with AIDS is to treat the underlying infection. Finally, although it is true that "[a] claim construction that gives meaning to all terms of the claim is preferred over one that does not do so," *Merck & Co. v. Teva Pharms. USA, Inc.*,

395 F.3d 1364, 1372 (Fed. Cir. 2005), that is a mere preference. It would be better to allow for some redundancy than to adopt a construction that is inconsistent with the invention. Thus, Lupin's generic ANDA product meets the "method for the treatment or prevention of the symptoms or effects of an HIV infection" limitation.

The Court will next consider claim 4 separately from the other method claims. Claim 4 depends from claim 2, which depends from claim 1. Those three claims follow:

> 1. A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises treating said animal with a therapeutically effective amount of a combination comprising [abacavir] or a physiologically functional derivative thereof, [AZT] or a physiologically functional derivative thereof, and [3TC] or a physiologically functional derivative thereof.
>
> 2. A method according to claim 1 wherein [abacavir] or a physiologically functional derivative thereof, [AZT] or a physiologically function derivative thereof, and [3TC] or a physiologically functional derivative thereof are present in a ratio of 1 to 20:1 to 20:1 to 10 by weight.
>
> 4. A method according to claim 2 wherein [abacavir], [AZT] and [3TC] are present in a ratio of 1 to 3:1 to 3:1 to 2 by weight.

The parties dispute whether the "physiologically functional derivative thereof" limitation of claims 1 and 2 is encompassed or excluded by asserted claim 4.[5] ViiV argues that dependent claim 4 encompasses that limitation, and thus that Lupin's generic product infringes the claim. Lupin disagrees, arguing that claim 4 has been narrowed to exclude the "physiologically functional derivative" limitation. Dependent claim 2 contains "physiologically functional derivative thereof" limitations for all drug compounds, but asserted dependent claim 4 does not. This would suggest that claim 4 does not encompass derivatives. Claim 13, which is also dependent from claim 1, and like claim 4, adds additional weight ratio limitations, follows:

> 13. A method according to claim 1 wherein [abacavir] or a physiologically functional derivative thereof, [AZT] or a physiologically functional derivative

[5] The Court construed "physiologically functional derivative thereof" as including "[a]ny physiologically acceptable salt[.]" (D.I. 126, p. 3). This means that abacavir sulfate would fall within the scope of the term.

> thereof, and [3TC] or a physiologically functional derivative thereof are present in a ratio of 1 to 10:1 to 10:1 to 5 by weight.

Claim 13 explicitly recites the derivative limitation, while asserted claim 4 does not. It would follow that claim 4 does not encompass the derivative limitation. The only conclusion that can be drawn from comparing asserted claim 4 with claims 2 and 13 is that claim 4 has been narrowed to exclude salt derivatives of abacavir, which would exclude Lupin's accused generic product. Lupin's generic product does not literally infringe claim 4.

As to the bulk of the method claims, ViiV argues that the reasons for finding non-infringement of formulation claim 47 do not extend to finding non-infringement of method claims 26, 27, 29, 30, 34, 36, 38, and 39. ViiV argues that the method claims are concerned with treatment, and the generic product ultimately treats the patient with abacavir. This gives rise to another discussion of *Merck & Co.*, 347 F.3d at 1367. On the surface, it would appear that because the asserted claims at issue are method claims, the situation becomes analogous to *Merck & Co.* This does make *Merck & Co.* a closer fit than it was with formulation claim 47. There are, however, still key differences between the singular method claim of *Merck & Co.* and the asserted method claims of the `191 Patent. In *Merck & Co.*, there was only a single asserted claim and the specification suggested that the salt form was understood as falling within the scope of that claim. *Id.* at 1371-72. Here, by contrast, there are unasserted claims that manifestly recite derivatives of abacavir that would include the salt forms. It would not seem true to the patentee's intentions of claim drafting for the Court to redefine and broaden the asserted claims as implicitly encompassing scope, where the patentee felt it necessary to explicitly claim that scope elsewhere. This is the most important distinction with *Merck & Co.*, as in that case, there was only a single method claim at issue, and construing that claim to include the salt form would not vitiate limitations in unasserted claims. Further, in *Merck & Co.*,

there was evidence that the lexicography of the patent defined the acid form of the drug as encompassing the salt form. *Id.* at 1372. Here, there is no suggestion in the patent that the chemical formula for pure or free base abacavir was specially defined to include the salt form. The inventors' explicit recitation of separate "physiologically functional derivative thereof" limitations in unasserted claims suggests they understood them to be different. Finally, Dr. Arnold persuasively explained how the salt form is chemically distinct from the pure or free base form of abacavir, and that the salt form offers superior functionality, and thus the Court cannot find that persons skilled in the art would have understood the pure or free base form of abacavir to be the same thing as, or to encompass, the salt form. (Tr. at 254-57). For these reasons, the instant case is distinguishable from *Merck & Co.*, and Lupin's generic product does not literally infringe the asserted method claims of the '191 Patent.

(iv) Infringement of method claims 4, 26, 27, 29, 30, 34, 36, 38, and 39 under the doctrine of equivalents

For similar reasons as to why the generic product does not infringe the formulation claim under the doctrine of equivalents, Lupin's generic product does not infringe the method claims under the doctrine of equivalents. Where the patentee explicitly claims certain subject matter in unasserted claims, that subject matter should not be transported into the asserted claims via the doctrine of equivalents. This, however, is what ViiV seeks here, as many unasserted claims contain the "physiologically functional derivative thereof" limitations, which would encompass the salt form of abacavir, yet the asserted claims do not. For this reason, Lupin's generic product does not infringe the method claims of the '191 Patent under the doctrine of equivalents.

II. OBVIOUSNESS

To determine obviousness, the Court must decide whether the subject matter of the claimed invention would have been obvious at the time the invention was made to a person of

ordinary skill in the art to which the subject matter of the invention pertains. 35 U.S.C. § 103(a). "Obviousness is a question of law with several underlying factual inquiries: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the field of the invention; and (4) objective considerations such as commercial success, long felt but unsolved need, and the failure of others." *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). Defendants have the burden of proving the obviousness of the claims by clear and convincing evidence. *Id.*

Defendants argue that the claimed combinations, abacavir and 3TC, and abacavir, 3TC, and AZT, were obvious in light of the prior art. Where a skilled artisan merely pursues known options from a finite number of identified, predictable solutions, the resulting invention is obvious under § 103. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012). "Where, however, a defendant urges an obviousness finding by 'merely throw[ing] metaphorical darts at a board' in hopes of arriving at a successful result, but 'the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful,' courts should reject 'hindsight claims of obviousness.'" *Id.* at 1070-71.

Teva asserts that the combination of abacavir and 3TC was obvious both because (i) a person skilled in the art ("POSA") would have been motivated to combine complementary and potent NRTIs to hit HIV early and hard, with a reasonable expectation that such a combination would suppress HIV reproduction and delay or prevent the development of resistant strains of the virus, and (ii) a POSA would have been particularly motivated to replace AZT in the AZT/3TC combination with abacavir, as abacavir was an NRTI, yet it avoided the toxicity problems

associated with AZT while still complementing 3TC. Lupin argues that a POSA would have been motivated to build upon the success of AZT/3TC by adding a third potent and low toxicity drug to the therapeutic regimen. ViiV disagrees, arguing that combination therapy was unpredictable, the sizeable universe of potentially useful drugs was inconsistent with an obviousness finding, problems of cross-resistance overrode considerations of potency and would have discouraged a POSA from combining abacavir and 3TC, and it made no sense to alter AZT/3TC by substituting abacavir for AZT, as AZT/3TC was the only known combination that worked.

(A) FINDINGS OF FACT

(i) Level of ordinary skill in the art.

The parties agreed that their definitions of a person skilled in the art are essentially the same. (Tr. at 1583). A person skilled in the art would have a medical degree or a PhD in virology or a related field in the biological sciences with experience in retroviral therapies. (Tr. at 79, Dr. Langer; Tr. at 309, Dr. Zingman).

(ii) Scope and content of the prior art.

(a) Background

The application leading to the '191 Patent was filed on March 28, 1996, and claims priority from two Great Britain applications filed on March 30, 1995, and claims inventions conceived in mid-1994. (JX 1, p.30). Human Immunodeficiency Virus ("HIV") was first reported in 1983, and was discovered to be the cause of Acquired Immune Deficiency Syndrome ("AIDS") in 1994. (Tr. at 1219-21, Dr. Ho). As a virus, HIV does its damage through replication. HIV (1) fuses and enters a cell; (2) converts viral RNA to DNA by reverse transcription; (3) integrates the new DNA into the host cell's nucleus; (4) uses the new DNA to

create copies of viral RNA and enzymes; (5) packages the new RNA and enzymes into virions; (6) buds from the cell; (7) cleaving, or cutting, the enzymes into their final form. (Tr. at 987-88, Dr. Larder; Tr. at 1278-79, Dr. Ho). AIDS, which is the final stage of HIV infection, is diagnosed where immune cells (CD4 T cells) fall below a certain level, and the patient is vulnerable to deadly opportunistic infections. (Tr. at 84, Dr. Blick). The AIDS epidemic was a public health crisis in the 1980s and 1990s, having left approximately 300,000 Americans dead. (PTX 258).

In 1995, the state of the art in HIV treatment was one of both failure and advancement, with drug researchers and doctors eager to identify effective therapies to halt the progression of the disease. (Tr. at 313-15, Dr. Zingman; Tr. at 1218-21, Dr. Ho). Nucleoside reverse transcriptase inhibitors ("NRTIs") were the first type of drugs developed for the treatment of HIV. (Tr. at 317, Dr. Zingman; Tr. at 1233-34, Dr. Ho). In order to incorporate itself into the nucleus of a host cell and induce replication, HIV must build a complete DNA chain from its RNA after entering the host cell. (Tr. at 1234-35, Dr. Ho). This is known as the reverse transcription process, and is mediated by an enzyme called reverse transcriptase.[6] (Tr. at 317, Dr. Zingman; Tr. at 1234, Dr. Ho). The DNA chain is made from four protein building blocks, which are known as deoxycytidine, deoxyguanine, deoxythymidine, and deoxyadenosine. (Tr. at 476, Dr. Parniak). They are generally referred to as the C, G, T, and A building blocks or bases. (Tr. at 476, Dr. Parniak).[7] NRTIs function as analogs of these building blocks. (Tr. at 477, Dr. Parniak). An NRTI will trick the reverse transcriptase enzyme into incorporating the drug into a growing viral chain. (Tr. at 1234, Dr. Ho). The NRTI then prevents further blocks from being

[6] It is "reverse" transcription because generally, DNA produces RNA, not vice versa.
[7] Each building block only binds with its pair: T binds with A, and C binds with G. (Tr. at 478, Dr. Parniak).

attached to the chain, thus acting as a "chain terminator" and halting replication. (Tr. at 482, Dr. Parniak).

AZT, the first FDA-approved anti-HIV drug, is an NRTI analog to the "T" DNA building block. (Tr. at 136, Dr. Blick; Tr. at 1220, Dr. Ho). AZT was known to be effective at decreasing mortality as a monotherapy, but for only a relatively short period of time. (Tr. at 327, Dr. Zingman). AZT also had the drawback of producing severe side effects due to its toxicity, causing patient compliance difficulties. (Tr. at 328, Dr. Zingman). Toxicity occurred because NRTIs may disrupt normal human DNA processes in a similar manner as to how they disrupt viral DNA. (Tr. at 328, Dr. Zingman). Other NRTIs were developed and used in treatment, but no drug provided sustained effectiveness when prescribed as monotherapy. (TTX 153; Tr. at 313-15, Dr. Zingman; Tr. at 1218-21, 1236-37, Dr. Ho). HIV replicates itself at a rapid pace, creating over one billion copies daily. (Tr. at 320, Dr. Zingman). The replication process is error-prone, allowing for millions of mutated variants created daily in an infected person. (PTX 353 at 126). HIV's ability to mutate rapidly causes the virus to become resistant to monotherapy in a matter of months. (Tr. at 982-83, 993, Dr. Larder; Tr. at 1237, Dr. Ho; Tr. at 445-46, Dr. Zingman; Tr. at 816, Dr. Arnold). Persons skilled in the art sought to solve the problem of treatment failure due to resistance. (Tr. at 991-93, 995-97, 1023-24, Dr. Larder; Tr. at 816, Dr. Arnold).

(b) Was combination therapy established as a treatment strategy as of March 1995?

The `191 Patent sought to solve the problem of viral resistance to monotherapy via NRTI combination therapy. `191 Col. 1:16-21. The claims of the patent recite two-drug and three-drug combinations, those combinations being abacavir and 3TC, and abacavir, 3TC, and AZT. *See* `191 Patent, claims 1-51. The effective filing date is March 30, 1995. The degree to which

combination therapy was accepted in the field of anti-HIV drug treatment as of March 1995 is relevant to the obviousness of the '191 Patent. *Novo Nordisk A/S v. Caraco Pharm. Laboratories, Ltd.*, 719 F.3d 1346, 1351 (Fed. Cir. 2013). Defendants argue that by March 1995, combination therapy had clearly begun to demonstrate its superiority to monotherapy. ViiV disagrees, arguing that there was still pervasive uncertainty in the field, and combination therapy was far from established.

The Court generally agrees with Defendants that combination therapy was emerging as superior to monotherapy in the field of HIV treatment, with the caveat that the field was still in the midst of considerable uncertainty. As early as June 1993, over a year and a half before the effective filing date, the *Journal of Commerce* reported on the Ninth International Conference on AIDS in Berlin. (TTX 153). The publication stated that "most AIDS cases now are treated with a combination of drugs because researchers believe this might be a better technique." (*Id.*). The failures of monotherapy were recognized: "The most critical point . . . is that no currently available monotherapy (use of one drug) will provide as long-lasting benefit as we would all desire." (*Id.*). The Hammer article from *Journal of Acquired Immune Deficiency Syndromes* reported that a "majority of panelists," *i.e.*, clinicians, would "recommend initial combination antiretroviral therapy" for a variety of patient types.[8] The Caliendo reference from *AIDS Commentary* also described the failure of AZT monotherapy (referring to its benefits as "transient") and the suspected superiority of combination therapy. (LTX 1490 at 516). The FDA had approved the ddC and AZT combination, and doctors independently prescribed AZT plus ddI. (LTX 1318; TTX 17; Tr. at 315; Tr. at 1361-62, Dr. Ho).

[8] These patient types were "treatment-naïve patients who are symptomatic and for treatment-naïve persons who are asymptomatic with less than 200 $CD4^+$ cells/mm.^{3} They would recommend combination therapy for patients who have had previous antiretroviral therapy and who are stable with <300 $CD4^+$ cells/mm^3 or who are progressing." (PTX 344 at S37).

All of these references strongly suggest that the field had been moving toward combination therapy prior to the effective filing date of the `191 Patent. This could be derived even without taking into account the results of the 3TC and AZT trials, presented at the 2nd National Conference on Human Retroviruses and Related Infections, held January 29 to February 2, 1995 in Washington D.C. (TTX 71). *AIDS Weekly* reported these results: "The combination of lamivudine (3TC) and zidovudine (AZT) has the most potent and longest lasting effect of any retroviral strategy yet tested in clinical trials, according to the result of four Phase II trials conducted in Europe and in North America." (*Id.*). This reference explicitly supports the premise that certain types of combination therapy were recognized as the best available treatment.

In arguing that combination therapy was not established, ViiV does cite a trial stating that monotherapy had "the best benefit for patients," but that trial came before the 3TC/AZT announcement and only touched upon the AZT and ddI combination. (PTX 440 at PB0261). It further is a single study of a single combination, which does not alter the fact that combination therapy was generally being pursued in the field. ViiV also cites the *The Medical Letter* in opposition, as that reference does state that monotherapy was the recognized preferential treatment, but even that reference suggested the suspected superiority of combinational therapy over monotherapy: "Concurrent use of two or more drugs may prove to be more effective than monotherapy." (PTX 251 at 87, 88, 90 n.1). Thus, the evidence is clear and convincing that combination therapy was generally thought to offer better treatment opportunities by March 1995.

(c) Universe of potential anti-HIV drugs for combination.

The size of the universe of potential drugs that a person skilled in the art would encounter when seeking an effective combination is relevant to the obviousness analysis. *See In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009). The more potentialities, the less likely that a particular combination is obvious. *Id.* Where options are fewer, indicia of obviousness increases. *Id.* Defendants argue that a person skilled in the art would look toward a small group of promising NRTIs for potential combinations, as NRTIs were the most effective and best understood class of drugs. ViiV disagrees, arguing that the universe was much larger than Defendants state, and that it certainly included drugs in classes other than NRTIs.

The Court finds that this factor weighs slightly against a finding of obviousness. It is true that good reasons existed to explore the NRTI category for combination research. As of the filing date, all four FDA-approved anti-HIV medications (AZT, ddI, ddC, and d4T) were NRTIs. (Tr. at 317-18, 321-24, Dr. Zingman; Tr. at 486, Dr. Parniak). The AZT and 3TC combination consisted of two NRTIs and was the first HIV therapy to offer lasting clinical benefits. (TTX 17, TTX 71; Tr. at 1381-82, 1391 Dr. Ho). Although evidence suggested that a particular mutational relationship between those two drugs gave rise to the combination's benefits (*see id.*), it would follow that persons skilled in the art would attempt to build on the success garnered from combinations in the NRTI class. At least one reference did show a special focus on NRTIs, with one researcher stating, "In the last year, there have been more clinical successes with [NRTIs] than with any other class of compounds." (TTX 224 at 45). "A powerful platform for drug discovery, in particular [NRTIs], may well set the stage for modifying the predestined pathogenesis of HIV-1." (*Id.* at 46).

All of this being said, however, the Court agrees with ViiV that a person of ordinary skill in the art would not completely limit herself to NRTIs in considering drug combinations. ViiV

rightly points out that, as of the time of filing, at least 28 drugs were in human clinical trials. (TTX 24; PTX 358; PTX 466; TTX 196; PTX 280; PTX 255; PTX 396; PTX 362; PTX 254; PTX 399; PTX 418; PTX 334; PTX 449; PTX 462; PTX 269; Tr. at 1231, Dr. Ho). Of these 28 drugs, thirteen were not NRTIs: eight were protease inhibitors ("PIs") and five were non-nucleoside reverse transcriptase inhibitors ("NNRTIs").[9] (Tr. at 1231-36). NNRTIs were thought to have the potential for less toxicity compared with the other drug classes, making them desirable research targets, especially considering the NRTI toxicity issue. (Tr. at 606, Dr. Parniak; PTX 491 at 103-04). PIs were identified as a "potent new class of drugs[.]" (PTX 251 at 88). Defendants argue, and Dr. Parniak testified, that problems with bioavailability and manufacturing would have discouraged research with PIs, but it was reported that, despite these difficulties, "there [was] still merit in pursuing the protease inhibitors[.]" (TTX 224 at 46). Dr. Parniak admitted that PIs were available for experimentation, and that he would consider combining NNRTIs and PIs. (Tr. at 604, 428).[10] Defendants' other experts made similar admissions. (Tr. at 428-29, Dr. Zingman; Tr. at 821-22, Dr. Arnold). Thus, the experts essentially agree that a person skilled in the art would not limit herself to NRTIs. As Lupin stated in its brief, "[s]cientists were eager for new drugs." (D.I. 202, p. 7). It makes sense for drug developers to pursue combinations in both the known and the less known classes, especially in what were still perilously uncertain days for HIV patients. Further, a patent application of one

[9] NNRTis, like NRTIs, focus on disrupting the reverse transcriptase step of HIV replication. Unlike NRTIs, NNRTIs do not mimic nucleosides and interfere with the growing DNA chain. They instead bind directly to the reverse transcriptase enzyme. (Tr. at 1233-35, Dr. Ho). PIs inhibit the "cleavage" step of viral replication by interfering with the protease enzyme. (Tr. at 1235-36, Dr. Ho).

[10] The fact that eight PIs were in clinical testing further undermines Dr. Parniak's position that the difficulty of manufacturing PIs would discourage clinical research for that class.

of ViiV's experts, Dr. Larder, specifically teaches that NRTIs could be combined with NNRTIs and PIs.[11] (*See* TTX 204). PIs and NNRTIs were on the table for combination therapy.

(d) Predictability of combination therapy?

The next inquiry into the scope of the prior art is the predictability of combination therapy. Defendants further argue that persons skilled in the art were armed with specific rationales that would lead them to the claimed combinations. Specifically, the AZT and 3TC combination's success would steer drug researchers to incrementally improve upon that combination to achieve predictable results. Teva argues that the AZT and 3TC combination would lead a person skilled in the art to combine abacavir and 3TC, as abacavir and 3TC would offer similar potency to the AZT/3TC combination, but with less toxicity. Lupin argues that the AZT/3TC combination would lead a person skilled in the art to improve the potency of that combination by adding abacavir. ViiV disagrees, arguing that the field was generally unpredictable, AZT and 3TC was the only known effective combination, but that effectiveness was due to a unique mutational interplay between the drugs. ViiV further argues that issues of cross-resistance would discourage combining abacavir and 3TC.

AZT, the first anti-HIV drug sanctioned by the FDA, had been approved for monotherapy since 1987. (Tr. at 1220, Dr. Ho). AZT was a potent inhibitor of HIV, but it produced toxic side effects severe enough to cause some patients to refuse it. (Tr. at 327-28, Dr. Zingman; TTX 56 at 736-37; TTX 78; TTX 202). Moreover, despite AZT's initial potency, the benefits of AZT monotherapy were short-lived. (*Id.*; Tr. at 1220, Dr. Ho). After a few months, the therapeutic benefit was lost due to the rapid emergence of a drug-resistant virus, resulting in treatment failure and patient death. (Tr. at 1220, 1237, Dr. Ho; PTX 128). Researchers looked to

[11] This supports Dr. Ho's testimony the PIs and NNRTIs began to show "safety and pharmokinetics data," and "efficacy results" before March 1995. Tr. at 1290.

alternatives for AZT in order to skirt the drug's resistance and toxicity issues.[12] 3TC's potency was similar to AZT's, yet it was much less toxic. (Tr. at 335, 345-47, 374, Dr. Zingman; TTX 56; TTX 224).[13] Like AZT, however, 3TC's initial therapeutic effectiveness as a monotherapy quickly waned. (Tr. at 423-24, Dr. Zingman). 3TC gave rise to resistance and was not effective as a monotherapy. (Tr. at 423, Dr. Zingman; Tr. at 1220, Dr. Ho). Three other NRTIs, ddI, ddC, and d4T, all failed as monotherapies due to the emergence of resistance in the virus. (Tr. at 1220, Dr. Ho).

All parties agree that the AZT and 3TC combination was a momentous development in the field. Results from the corresponding trials were described as a "breath of fresh air," and the combination was said to offer "the most potent and longest lasting effect of any antiretroviral strategy yet tested in clinical trials." (TTX 71 at 2; Tr. at 339, Dr. Zingman). AZT and 3TC effectively delayed the emergence of resistant strains of HIV, even though neither drug did so individually. (*Id.*; TTX 224; TTX 300; Tr. at 337-39). The efficacy of the 3TC and AZT combination was thought to depend upon a mutation in the M184 reverse transcriptase gene that made the virus resistant to 3TC, but overrode mutations conferring AZT resistance, thus resensitizing previously AZT-resistant HIV to the antiviral effects of AZT. (TTX 71 at 3).[14]

Defendants argue that good reasons existed to focus on abacavir as a low toxic and potent candidate for combination therapy. ViiV disagrees, arguing that there was no reason to focus on abacavir among the myriad of available compounds. Abacavir is an analog of another then experimental anti-HIV drug known as carbovir. Both drugs metabolize to the same antiviral

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[12] "Drug resistance and bone marrow toxicity point to a need for new chemotherapeutic agents with high antiviral potency and low myelotoxicity for use as alternatives to, or in combination with, AZT." (TTX 78 at 437).
[13] 3TC was also much less toxic than ddC, another FDA-approved NRTI, despite the structural similarities between those two drugs. (TTX 224 at 45).
[14] "Researchers 'speculate' that 3TC may increase AZT's effectiveness by delaying viral resistance to the drug." (TTX 17 at 12).

form in the body, carbovir triphosphate, albeit via different routes. (TTX 265, Abstract I84; Tr. at 515, 586, Dr. Parniak; Tr. at 1373-74, Dr. Ho). Both are "G" analogs. (*Id.*). Carbovir was reported to be a potent inhibitor of HIV and to have synergistic *in vitro* activity with AZT (a "T" analog) and ddC (a "C" analog). (PTX 438 at 967; TTX 93 at 2-3; TTX 228 at 90-92). Carbovir was discussed in the prior art as a potential alternative to AZT. (Tr. at 558-61, 586, Dr. Parniak; TTX 78 at 437). ViiV argues that carbovir's poor oral bioavailability and reported toxicity in dogs caused drug developers to abandon it, and they likewise would have looked away from carbovir's analog, abacavir. It is true that carbovir had poor bioavailability, and in one reference, was reported to cause toxicity in dogs. (PTX 438 at 967; Tr. at 515-17, 599, Dr. Parniak; TTX 93; TTX 228). However, this did not apply to abacavir, because abacavir was known to offer sufficient oral bioavailability and to be non-toxic in laboratory animals. (TTX 265 at I6, I86, I88; Tr. at 352-53, Dr. Zingman; Tr. at 1375-76). Dr. Ho testified that carbovir's toxicity report would be a "red flag" to researchers investigating abacavir, but he also admitted that a researcher would understand that toxicity issues would be resolved were a drug in phase 1 trials. (Tr. at 1294, 1377-78). As of October 1994, abacavir was in Phase I human clinical trials. (TTX 196; TTX 116 at § 8). Carbovir's toxicity would not have been imputed to abacavir.

ViiV argues that a person skilled in the art had no reason to focus on abacavir in particular. ViiV points out that the first abacavir data was not published until October 1994 at the "ICAAC" conference, and that abacavir was only described in five out of more than a thousand abstracts presented at that conference. (Tr. at 442-43, Dr. Zingman; TTX 265). One publication reciting the major points of the conference, however, specifically highlighted "Wellcome's 1592UB9," *i.e.*, abacavir. (TTX 196). This suggests that abacavir stood out among the topics covered at the conference. ViiV also argues that abacavir's potency was in

doubt, as one study showed that abacavir was 50 to 100 times less potent than AZT. (TTX 265 at I82). The weight of the scientific literature, however, shows that abacavir was comparably potent to AZT. (TTX 78; TTX 265 at I82; TTX 258 at 2:65-68, Tr. at 511-17, 559-61, 581, Dr. Parniak). Abacavir also had lower toxicity than AZT, was synergistic with other compounds, and penetrated the central nervous system, which is a desirable feature for an anti-HIV medication. (*Id.*). Abacavir was reported to have *in vitro* synergistic activity with AZT, ddI, and ddC. (TTX 265 at I6). Abacavir was reported to be "an attractive candidate for clinical evaluation." (TTX 265 at I6, I88). It was also "an important candidate for further development as an anti-HIV drug for combination therapy," due to its "cross-resistance profile and the relatively slow emergence of resistance." (TTX 265 at I82). Thus, the evidence shows that abacavir would have been a ripe candidate for researching new combination therapies.

Defendants argue that because the AZT and 3TC combination was the best known combination, and abacavir was known as a particularly strong candidate for future combinations, the claimed combinations bringing those drugs together were obvious. ViiV argues that the fact that all combinations other than AZT and 3TC had failed showed the extreme unpredictability of the field. Defendants point to other allegedly successful combinations to show that it was not an unpredictable field. Defendants rely on the `191 Patent's specification to show that AZT was known to combine well with other compounds. The specification states, "The combination of [AZT] with either ddC or ddI has shown promising results in HIV infected patients[.]" `191 Col. 1:66-67. ViiV points out that the studies relied on in the specification for this statement were outdated by March 30, 1995, and that it was understood that those combinations were in fact not

effective. Defendants counter that admissions in the specification regarding the prior art are binding on the patentee.[15]

The Court accepts the statement that AZT plus ddI or ddC were regarded as "promising." That is not the same thing as saying they were effective. Defendants themselves, however, cite references that contain statements indicating that those combinations were not effective long-term. It would not make sense for the Court to allow Defendants to rely on those references where they support the obviousness case, but to pretend that certain statements unfavorable to the obviousness analysis do not exist. *AIDS Weekly* from February 1995, a Teva exhibit that Defendants rely on to show the success of AZT and 3TC, also discusses the AZT/ddC Phase II trial. (TTX 71 at 5). That trial showed that therapeutic benefits of AZT/ddC were not sustained at 24 weeks. (*Id.*). The Hammer reference, which is both a ViiV and Lupin exhibit, is relied on by Defendants to show the general acceptance of combination therapy and to support the theory that potency was understood to lessen the problem of resistance. (LTX 1324; PTX 344; D.I. 205 at 15). That reference also explains that no combination therapy, including AZT/ddC and AZT/ddI, had been shown "beneficial in delaying *clinical* disease progression or in improving survival." (*Id.* at S28) (italics in original). As to whether Hammer supports Defendants' position that potency was understood to be the most important factor, Dr. Hammer did state, "Perhaps it is better to hit as hard as you can as early as you can," and the general consensus was that combination therapy should be started earlier rather than later in treatment. (*Id.* at S36). There is nothing in Hammer, however, that suggests that combination therapy was predictably effective.

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[15] The cases that hold that an admission in the specification is binding on the patentee typically involve a situation where the patentee attempts to deny the existence of something in the prior art. *See, e.g.*, *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1362 (Fed. Cir. 2007), a case where expert testimony was given that stem cells had not yet been proven to exist in umbilical cord blood by the asserted patent's filing date, despite the statement in the specification that stem cells were concentrated in cord blood at a much higher level than in adult blood. *Id.* at 1361-62. In contrast, the '191 Patent's specification only states that AZT plus ddC or ddI garnered "promising results," which is far from a definite statement as to the ultimate effectiveness of those combinations.

It in fact suggests strongly otherwise, as there was not even any proof of "clear-cut clinical benefits" of combination therapy. (*Id.* at S36). Doctors "could not recommend one combination over another based on current data." (*Id.* at S34). Defendants' own physician expert admitted that he regarded antiretroviral therapy to be "quite confusing" in 1995. (Tr. at 762, Dr. Laurence).

Defendants also rely on results from the "Thompson" study that indicated that AZT plus ddC or ddI afforded greater survival benefit than did starting on AZT and then switching to ddC or ddI. (*Id.*). According to Defendants, these results, juxtaposed with what was known about AZT/3TC, suggest the obviousness of the claimed combinations. Defendants, however, admit that no definitive conclusions could be drawn from this study, as it was a retrospective (or "look-back") study rather than a prospective study, and that prospective studies were much better.[16] (Tr. at 747, 48). Later prospective studies showed that AZT and ddI provided no better results than monotherapy, or, in the case of AZT and ddC, produced worse results. (Tr. at 1246, Dr. Ho; PTX 420; PTX 440 at Abstract PB0261; Tr. at 633, Dr. Parniak; PTX 268 at PB0266; PTX 344).[17] It was also known that AZT combined with ddC showed signs of increased incidence of serious toxicity in patients in advanced stages of the disease. (PTX 432 at 4253; Tr. at 1246-47, Dr. Ho). Other combinations, including AZT and interferon, and AZT and nevirapine, did not display good results. (PTX 315 at 059B; PTX 344 at 0012152-53).

The AZT and 3TC combination was the only therapy known to provide prolonged viral load reduction and increase in CD4 count as of the priority date. (TTX at 17; TTX at 71; TTX 224). No other combination was recognized as providing sustained therapeutic effects. As one

[16] Dr. Ho elaborated on the weaknesses of retrospective studies. (Tr. at 1242-43).
[17] Defendants argue that AZT/ddI combination was superior to monotherapy. The weight of the evidence, however, is against that proposition.

reference stated, that combination was a "breath of fresh air" to the field, *i.e.*, it provided something sorely lacking. (TTX at 71). The high degree of failure suggests that combination therapy could not be considered a predictable field.

Defendants argue that the claimed combinations are obvious in part because each of abacavir, 3TC, and AZT is an analog to a different DNA building block (the C, G, and T bases, respectively). These blocks are essential to the reverse transcription process and thus HIV's ability to replicate. Because each drug would inhibit replication at different sites of the growing viral DNA chain, they would not compete with one another to effectuate their anti-HIV activity. Defendants argue that the combination of differing analogs was understood to provide synergistic (or at least additive) effects. Defendants argue that persons skilled in the art knew of the beneficial nature of combining NRTIs operating on different sites of the DNA chain, and would thus be motivated to combine the claimed combinations with a reasonable expectation of success. ViiV disagrees, arguing that Defendants provide no evidence that persons skilled in the art were aware of the beneficial nature of the specific drug interactions at play.

In support of this position, Defendants rely on the testimony of their experts. Dr. Zingman testified, "By March of 1995, we already had pretty good evidence that it would be helpful to have complementary nucleoside reverse transcriptase inhibitors, and that would be one way to put them together as a combination." (Tr. at 326). "[W]e started to get information about potential antagonism between the cytosine analogs, so we started to get information that it wasn't a good idea to use two T drugs, for example[.]" (Tr. at 334). He testified as to an expectation for success: "[T]he potential to join abacavir and 3TC because one was a G analog and one was a C analog and that you'd expect they would work well together." (Tr. at 376). Dr. Zingman continued that "combination therapy targeting different DNA bases was already established as a

treatment option for people with HIV infection." (Tr. at 379). Dr. Parniak echoed Dr. Zingman's opinion, testifying in great detail as to how the strands of DNA are made in the reverse transcription process, and how the component drugs work to terminate the DNA chain, and explaining the expected benefit derived from combinations where the analogs do not compete for the same site on the DNA chain. (Tr. at 477, 482-86, 516).

Aside from expert testimony, however, Defendants do not provide a single reference to support the premise that combining analogs of different bases was known to provide a more potent combination. It is true that certain combinations having different bases (at least AZT and 3TC) were reported as offering significant clinical benefits. Defendants, however, do not cite a single reference or publication reporting that the therapeutic benefits of combination therapy could be explained by the drugs affecting different bases of the DNA chain. Nor did Defendants' experts rely on any references in support. Dr. Zingman testified that "we had pretty good evidence" that combining NRTIs with complementary bases was known to be effective, yet he never actually identified that evidence. Likewise, Dr. Parniak testified that it was known that certain combinations having two NRTIs with different bases provided additive to synergistic inhibition of HIV replication, but he never provided any studies or publications suggesting this was the case. In fact, his deposition testimony was that he could not identify any references that taught to combine compounds with different bases.[18] There is no reference in the record showing that such a sophisticated understanding of combination therapy existed as of March 1995.

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[18] "Q. And but my question focused on whether there was a general statement in the literature before March 30, 1995 that taught to combine combinations of compounds of different bases and said that they would lead to additive to synergistic effects? Can you identify any such references for me?

A. Off the top of my head, no, I cannot. I would have to conduct an extensive literature review."

Tr. at 612-13.

Lupin cites Schinazi 1995 for the field's supposed recognition that NRTIs with the same mechanism of action should not be combined, but that reference in no way refers to the benefits of combining NRTIs with different analog bases. It is instead concerned with the discovery that structurally similar NRTIs may differ significantly in regard to levels of toxicity.[19] Lupin also cites *AIDS Weekly 1995* for the proposition that researchers realized that if the success of the 3TC and AZT combination was "due to specific interactions, it may lead to rational strategies for combination therapy instead of random choices from a wide array of drugs." (TTX 71 at 2). This article, however, specified the M184V mutation selected by 3TC and the consequential resensitization of the virus to AZT as the reason for the 3TC and AZT combination's success. (*Id.* at 3). Thus, the specific interactions from which scientists might learn rational strategies for combination involved mutational interplay, not interactions derived from differing DNA bases. If the benefit of offering combinations with different DNA bases were truly known in the art prior to the filing date, one would imagine some reference, somewhere, would have said so, and been presented during the trial.

ViiV also rightly points out that researchers did combine NRTIs targeting the same nucleoside bases, including 3TC and ddC, up until shortly before the filing date, and some NRTI combinations with analogs of different bases failed to show any benefit over monotherapy or even displayed antagonistic qualities. (TTX 71 at 4, 5; Tr. at 920, Ms. St. Clair; PTX at 178). These failures provide further reason to doubt that combining analogs of different bases was a known method of increasing potency, although it is Defendants' failure to provide any references

[19] "We are realizing that nucleosides are the only approved antiretroviral drugs and that they are not all the same. For example, although structurally related to ddC, 3TC does not cause peripheral neuropathy even at high doses, thus destroying the fallacy that there is no 'non-toxic nucleoside' for retroviral therapy." (TTX 224 at 5).

in support that is the most important factor in reaching the conclusion that the Defendants have not proved that it was a known method.

Defendants cite testimony from Dr. Ho in an attempt to show that he agreed with their position that combining analogs with different DNA bases was an established treatment strategy as of the filing date. The Court does not agree with this interpretation of the testimony. Although Dr. Ho testified that one might avoid using the same nucleoside analog based on the same building block, he also testified that combining different analogs was just a theory. (Tr. at 1252). "In terms of what might work, in my opinion this is unpredictable, what may turn out to be synergistic, antagonistic, or additive. Until one does the experiment, it's not --- the outcome is not known." (*Id.*). At best, it has been established that one might avoid combining drugs that work on the same base, but there is no proof that a person skilled in the art had any expectation that combining drugs of different bases would offer additive or synergistic potency.

(e) Teaching away and cross-resistance

The parties debate the significance of cross-resistance. ViiV argues that the art taught away from using abacavir in a combination with 3TC because those two drugs share overlapping cross-resistance profiles. ViiV also argues it would make no sense to remove AZT from the AZT and 3TC combination, because that combination was understood to work due to specific mutational interplays. Defendants disagree, arguing that cross-resistance was not a factor where highly potent combinations were concerned, and that in any event the cross-resistance between abacavir and 3TC was not significant. As to the particular combinations, Teva argues that it would be obvious to remove AZT from the AZT/3TC combination and replace it with abacavir, as abacavir offered similar potency to AZT with lower toxicity. For its part, Lupin argues that it

would be obvious to combine 3TC, abacavir, and a low dose of AZT, as persons skilled in the art knew this would provide an extremely potent therapy with an acceptable degree of toxicity.

There is no dispute that drug resistance was the reason behind the failure of NRTI monotherapy. (*See, e.g.*, PTX 128). "The development and clinical use of selective inhibitors to treat human immunodeficiency virus (HIV) infection have been marred by the ability of the virus to become drug resistant []." (*Id.*). HIV's ability to replicate up to one billion times per day, combined with its propensity to err in the transcription process, allow for millions of viral variants or mutations each day. (Tr. at 789, 803, 816, Dr. Arnold; Tr. at 1219-20, Dr. Ho). In other words, NRTI monotherapy selected for HIV mutations that resulted in resistance to the drug. (Tr. at 368-69, Dr. Zingman; Tr. at 490-91, Dr. Parniak). Monotherapy provided temporary benefits until the resistant variants emerged, causing the therapy to lose effectiveness. (PTX 128). This occurred with all NRTI monotherapies, including AZT and 3TC individually, without regard to their individual potency. (Tr. at 789, 803, 816, Dr. Arnold).

The hope in the field was that combination therapy would succeed where monotherapy failed. At the time of filing, there was only one combination known to provide sustained therapeutic benefits for HIV-infected persons: AZT and 3TC. The success of this combination was a breakthrough in the art, coming a few months prior to March 1995. (TTX 17; TTX 71). Although the pharmaceutical and viral interactions were not entirely understood,[20] the prevailing thought behind the combination's success was 3TC's selection of the M184V mutation, which appeared to restore the effectiveness of AZT in an AZT-resistant person. (Tr. at 796, 823, Dr. Arnold; Tr. at 1004, Dr. Ho; Tr. at 1003-04, Dr. Larder; TTX 71). In other words, it was

[20] "Researchers speculate that 3TC may increase AZT's effectiveness by delaying viral resistance to the drug." (TTX 17 at 12).

suspected that the mutations selected for by 3TC and AZT interacted with one another to make a previously resistant infection treatable. This is what allowed the combination to provide sustained therapy where other treatments failed.

Defendants point out that the mutational interplay was unproven, but it was by far the best explanation given for the combination's success in the prior art.[21] As the AZT and 3TC combination was a turning point in the field of HIV therapy, it would seem a POSA seeking to mimic its success would invariably put stock into the only known explanation for that success. The explanation hinged on the resistance profiles of the individual compounds of the combination, which would make cross-resistance highly significant. That is not to say that Defendants are incorrect when they assert that potency was a fundamental principle of compound selection.[22] There was the hope that potent combinations would delay the emergence of a resistant virus. The fact that potency was essential to therapy, however, is not inconsistent with a strong desire to avoid cross-resistant combinations, as drug resistance might undermine potency altogether. (Tr. at 1018-19, Dr. Larder). Defendants also cite TTX 108. It shows that when using certain potent combinations *in vitro*, "no resistant variants emerged." (TTX 108 at 195S). Defendants thus argue that it was known that potency could trump resistance. There is no evidence, however, that those combinations had overlapping cross-resistance profiles, and they thus do not speak to the issue. Further, it was later known that the combinations of AZT/ddI and AZT/ddC, which showed very strong potency *in vitro*, did nothing to delay resistance clinically. (LTX at 1490 at 518-19). Defendants argue that research was conducted on

[21] Teva notes that TTX 71 stated that "the efficacy of 3TC apparently goes beyond its ability to prolong the efficacy of AZT," but that exhibit clearly singles out the mutational interplay as the main suspected reason behind the combination's success.

[22] It seems obvious even to a layperson that a more potent drug is superior to a less potent drug for treatment of a disease, all else being equal.

combinations that included both ddI and 3TC, drugs with known overlapping cross-resistance profiles. (LTX 1518 at 953-54). This research was conducted prior to the announcement of the AZT and 3TC trials, which everyone agrees was a monumental occurrence in the field, and the Court sees it as a strongly indicating the importance of accounting for cross-resistance.

Defendants also rely on the testimony of Dr. Laurence, who stated, "You want to target it early on in infection with the most potent combination you have, so that you don't have to worry about resistance or cross-resistance . . . [h]it it hard and hit it early." (Tr. at 672-73, 678). There was, however, little evidence that hitting the infection hard and early with combination therapy made cross-resistance a non-issue. Defendants point to the Hammer reference for the proposition that "the overriding goal of researchers by March 1995 was . . . to hit HIV 'hard' and 'early.'" Although clinicians in the reference discuss the need to use maximum dosages, and tentatively suggest that combination therapy might best be used right away, rather than in later stages of infection, the tone and tenor of the article does not inspire confidence. (*See* PTX 344 at S36). To the contrary, the reference highlights the uncertainty in combination therapy, stating, "many issues complicate[d] the evaluation of combination therapy for HIV." (*Id.* at S25). A "clear-cut clinical benefit" demonstrating combination therapy's superiority to monotherapy had yet to be proven.[23] (*Id.* at S36). Clinicians did not understand why some studies showed promise, while other studies disappointed.[24] One lingering question was "[w]hat will the impact of combination therapy be on the emergence of resistance and cross-resistance?" (*Id.* at S25). The Hammer reference thus does not suggest that any principles of combination therapy had

[23] This reference was circulated prior to the publication of the AZT/3TC combination results.

[24] "Salvage studies, such as ACTG 116B/117, have seemed promising in terms of continuing the antiviral effect by switching therapy. Yet the results of ACTG 155 were disappointing. Why did the salvage studies work and ACTG 155 not work?" (*Id.*).

been thoroughly established, and in no way suggests that potency resolved issues of cross-resistance.

ViiV also cites three references teaching that cross-resistance was to be avoided in selecting compounds for combination. (TTX 225 at 172; PTX 365; PTX 434). Defendants dispute the interpretation of these references as containing statements teaching against combining drugs with overlapping profiles of cross-resistance. (*See id.*). Defendants argue that TTX 225 emphasizes toxicity concerns, not cross-resistance, as it states, "if synergistic toxicity is not a problem, then these should be combined with drugs that impact acute infection." (TTX 225 at 172). That same paragraph, however, flatly stated that "drugs should not be cross-resistant." (*Id.*; Tr. at 1009, Dr. Larder). It thus clearly teaches against combining cross-resistant drugs.

Defendants also argue that the second reference, PTX 365, stresses potency and selectivity, and lists cross-resistance toward the end of its teachings, thus suggesting that factor is less important. That reference lists various factors as important when combining drugs, including "the stage of HIV replication at which the agent works," "the pharmokinetic profile," "penetration into the central nervous system," and "the likely toxicity profile" before noting that "[a]nother increasingly important issue is the potential for inducing resistance and the likelihood of cross-reactive resistance with other agents." (PTX 365 at 202). The order factors are listed, however, is not determinative of their value. Further, the recognition that choosing drugs for combination is a complicated endeavor that requires the weighing of many factors does not suggest that cross-resistance is a minor factor. There is no dispute that clinicians sought to obtain the best balance of high potency and low toxicity. The question is the significance of cross-resistance's potential to undermine therapeutic value in choosing compounds to combine. This reference's acknowledgment that cross-resistance is an "increasingly important issue"

speaks for itself. Finally, the third reference, PTX 434, states that knowledge of 3TC's selection for the M184V mutation would "permit effective patient monitoring for the development of resistance to these drugs and to design rational drug combinations." (PTX 434 at 880). As Defendants point out, PTX 434 discusses the importance of maximizing antiviral effects while minimizing toxicity. (*Id.*) It also straightforwardly pairs the rationality of combining drugs with knowledge of resistance. (*Id.*). Even the most potent combination, AZT and 3TC, which were not cross-resistant, still rapidly selected for the M184V mutation. (PTX 363 at LB33; Tr. at 1003, 1018-19, Dr. Larder).

The weight of the prior art most strongly suggests that concerns of cross-resistance would be a discouraging factor, even for combinations displaying significant potency and limited toxicity. HIV's ability to mutate quickly gave rise to the difficulties in identifying an effective treatment. It was recognized that "the enormous potential of HIV-1 for the development of drug resistance cannot be denied." (TTX 224 at 45). Drug resistance was the root cause of the failure of both monotherapy and combination therapies prior to the AZT and 3TC combination, and the best understanding of why that combination worked was attributed to how it selected for mutations, *i.e.*, its resistance profile. (Dr. Larder, Tr. at 1018-19, 1029). Drugs with issues of cross-resistance retained the potential to undermine even the most potent combinations. Thus, resistance profiles would be a critically important factor in forming combinations, notwithstanding the fact that toxicity and potency were also vitally important.

Cross-resistance might discourage a person skilled in the art from pursuing a particular combination, but would it discourage the specific combination of 3TC and abacavir? Defendants argue that it would not, as the cross-resistance between those two drugs was minimal, and there were strong countervailing reasons to combine those drugs. ViiV argues that the cross-resistance

between 3TC and abacavir was known and significant, and persons skilled in the art would have accordingly avoided that combination.

3TC and abacavir both select for the M184V mutation, a mutation that can cause resistance to HIV.[25] (Tr. at 1016-18, Dr. Larder). Abacavir's selection of the M184V mutation caused increases of resistance at levels between two and five-fold. (TTX 265 at I82; Tr. at 552-54, Dr. Parniak). Defendants argue that resistance at those levels is not significant, while ViiV argues that it would be discouraging. Dr. Parniak testified that two-fold resistance was not significant, and five-fold resistance was "borderline at best." (Tr. at 553-54). Defendants point out that this is consistent with a 1998 article by Dr. Larder that defined "resistance" as greater than five-fold, and "high-level resistance" as greater than ten-fold. (LTX 1341; Tr. at 1348). In 1993, Dr. Larder also described five-fold resistance as low resistance. (PTX 128 at 5653, 5655). Despite abacavir's cross-resistance with ddI and ddC in the range of a three-to-six fold increase, abacavir was declared "an important candidate for further development as an anti-HIV drug for combination therapy," due to a lack of cross-resistance with AZT, its synergy with ddI, ddC, and AZT, and the slow emergence of resistance. (TTX 265 at I82; Tr. at 358-60, Dr. Zingman; Tr. at 444-45, 551-55, Dr. Parniak). AZT, ddI, and 3TC were combined and evaluated as having "superior activity" *in vitro*. (LTX 1484 at 268; Tr. at 701, Dr. Laurence; Tr. at 809-10, 833, Dr. Arnold). They were also combined and used in clinical trials that suggested therapeutic intervention at an earlier stage of HIV infection. (LTX 1484 at 265, 268; Tr. at 702-04, Dr.

[25] Although the M184V mutation causes a degree of resistance to both 3TC and abacavir, it ironically reverses resistance to AZT.

Laurence). This was despite the fact that ddI and 3TC have cross-resistance to some of the same mutations as abacavir and 3TC.[26] (LTX at 1484 at 265, 268; Tr. at 1041, Dr. Larder).

In response, ViiV first notes that abacavir did not only select for the M184V mutation, it also selected for secondary L74V and K65R mutations, which also conferred resistance to 3TC. (TTX 265 at I82; Tr. at 1016-17, Dr. Larder). Defendants' own expert, Dr. Zingman, described the resistance conferred by these latter two mutations as "significant." (Tr. at 360). Dr. Laurence, another expert of Defendants, testified that abacavir and 3TC would have appeared to be cross-resistant on their face, and that combination therapy was confusing in general. (Tr. at 763-64). Although the Tisdale reference (TTX 265 at I82) described the emergence of the M184V mutation to abacavir as slow, both Drs. Larder and Arnold testified that the four passages required for abacavir to select the M184V mutation was quick. (Tr. at 1015-16; Tr. at 820). There is a reference suggesting that levels of resistance between two and six were not insignificant, as resistance at similar levels affected the clinical use of ddI.[27] (Tr. at 1269-70, 1275-76, Dr. Ho). Dr. Ho testified that although it is true that researchers did pursue the ddI and 3TC cross-resistant combination, only 3TC and abacavir had completely overlapping resistance profiles. (Tr. at 1297-98, 1365-66, Dr. Ho).

Abacavir was declared an important candidate for combination therapy due to its general cross-resistance profile and its synergy with other NRTIs in the Tisdale abstract. It thus was a good candidate for combination therapy generally. The cross-resistance profile, however, also

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[26] Dr. Arnold referred to the St. Clair abstract in his testimony on this subject, which was outside the scope of his expert report, and thus cannot be considered here.

[27] PTX 696 notes that ddI was shown to confer resistance in patients who received long-term therapy, while also noting that "[i]t has been difficult to detect more than a 2 to 8 fold difference in [ddI] susceptibility…which is in contrast to the high-level [AZT] resistance (e.g., 100-fold changes from the baseline seen after prolonged [AZT] therapy[.]" (PTX 696 at S144; Tr. at 1269-70). "The clinical significance of the detection of [ddI] resistance in vitro remain[ed] unclear." (*Id.*).

gave reasons to look in directions other than combining abacavir with 3TC. Although a fold increase of between two and five was not considered extremely high, it would at a minimum factor into the consideration, especially in conjunction with the knowledge that other drugs (ddI in particular) displaying resistance between two-fold and eight-fold resulted in treatment failure. As to the Dr. Larder publications relied on by Defendants, one was published in 1998 and thus is not relevant here, as it is fair to believe that much was learned about M184V cross-resistance three years after AZT/3TC and the claimed combinations entered the public sphere. The other publication, from 1993, characterized ddC's five-fold resistance as "partial resistance," and resistance at levels of less than five-fold resistance as "low-level."[28] (PTX 128 at 5653, 5655). The countervailing evidence, however, that the overall cross-resistance profile was expected to be capable of interfering with anti-HIV therapy is persuasive, especially the testimony of Defendants' own witnesses, Dr. Zingman and Dr. Laurence.

The existence of research into the ddI and 3TC cross-resistant combinations tends to show that cross-resistance would not always conclusively rule out research on a particular combination. That being said, Defendants did not counter the evidence showing that the degree of cross-resistance between 3TC and abacavir was more extensive than between ddI and 3TC. It is also important to view all of the testimony in light of the treatment situation during the early to mid-90s. Drug researchers and physicians acted in the midst of a public health crisis, and they did not have a strong understanding as to what would work and why. The situation was desperate, and with doctors scrambling for solutions, they might not be inclined to rule out any

[28] ViiV argues that Defendants' failure to cross-examine Dr. Larder on his own publications that allegedly undermine his testimony justifies an inference that Dr. Larder's answers would have explained away any inconsistencies. I do not find that any choice not to ask a witness a question justifies an inference that the unasked question would have been answered unfavorably to the party who did not ask the question. Defendants, however, do not appear to use the reference to specifically impeach Dr. Larder's testimony, for had they, they would have violated Fed. R. Evid. 613(b) for failing to give him the chance to explain or deny the statement. They instead use it as one prior art publication supporting their position that the resistance conferred by abacavir was not significant.

particular combination absent experimental evidence indicating that it should not be pursued. The fact that in certain instances researchers pursued potential solutions in the face of teachings suggesting that the solution might not work is not surprising in this context. That does not change the fact that those teachings existed, and would have been informative for those seeking to combine drug compounds. The cross-resistance between abacavir and 3TC is a significant difference with the prior art AZT and 3TC combination. In the end, the cross-resistance profiles of abacavir and 3TC provided a reason for researchers to look in another direction than a combination of those drugs.

(iii) The claimed combinations in comparison with the prior art.

The Court will next address the specific claimed combinations and the differences and similarities between those combinations and the prior art.

(a) The double combination: abacavir and 3TC.

Teva argues that, because abacavir showed synergy in combination with ddC, 3TC was a logical replacement for ddC, as ddC and 3TC had identical mechanisms of action, yet 3TC had a superior therapeutic window and toxicity profile. Teva argues that persons skilled in the art would have known that replacing ddC with 3TC would have led to predictable therapeutic benefits, because both ddC and 3TC are "C" analogs, and thus work on a different base than abacavir. It has already been shown, however, that no references in the prior art support the position that drug researchers understood this phenomenon. There is thus no justification for the premise that drug researchers would expect another "C" analog to combine well with abacavir. Further undermining Teva's position is the fact that, to reach this conclusion, Teva chiefly relies on Dr. Parniak's discussion of Du 1992 (TTX 78), Daluge 1994 (TTX 265), Coates 1992 (TTX 56), and Hart 1992 (TTX 124). (Tr. at 581-82, 587; D.I. 205 at p. 10). This combination,

however, was not disclosed in his expert report as one of the specific combinations that he relied upon to form the foundation of his obviousness opinion. In his report, Dr. Parniak defined the following two groups of references as each separately supporting his obviousness opinion: (1) AIDS Alert 1995 (TTX 17), Du 1992 (TTX 78), and Daluge 1994 (TTX 265) and (2) New AIDS Therapy 1992 (TTX 196) and Hart 1992 (TTX 124). (*See* D.I. 211, Exh. A, *Dr. Parniak's Expert Report* at ¶ 353). The Court was clear that witnesses were to testify only to combinations specifically identified in their expert reports as supporting their opinions.[29] Dr. Parniak thus was not permitted to mix and match between his identified groups as he did in his testimony, where he relied on Hart 1992 (from the second group) in combination with Daluge 1994 and Du 1992 (from the first group). Further, he explicitly relied on Coates 1992 (TTX 56) in forming his opinion, which does not appear in either of the two groups. (Tr. at 636). For this reason, Dr. Parniak's testimony on this point will not be considered by the Court.[30]

Teva also argues that a person skilled in the art would seek to improve upon the AZT/3TC combination by removing AZT and replacing it with abacavir. It is true that abacavir and 3TC were "second generation NRTIs," less toxic than AZT, a first generation NRTI. (TTX 265 at IG, I82; TTX 56). It is also true that abacavir and 3TC were understood to be potent inhibitors of HIV, and both had been shown to have synergy with other NRTIs. (TTX 196; TTX 202). Despite all of this, to remove AZT from the AZT/3TC combination and replace it with abacavir would be inconsistent with the best understanding of why that combination worked. Although the pharmaceutical and viral interactions were not entirely understood, the prevailing thought behind the combination's success was 3TC's selection of the M184V mutation, which

[29] "If I find something in [the expert report] saying, here are 27 references. It's some combination of these that makes it obvious. Well, if that's what the report says, that's not good enough." (D.I. 188, p. 46 ll. 11-15).
[30] Dr. Parniak's testimony on this point was thus in violation of Fed. R. Civ. P. 26. ViiV timely objected. (*See* Tr. at 569-592) The Court now grants ViiV's motion to strike (D.I. 211) this testimony.

appeared to restore the effectiveness of AZT in an AZT-resistant person. (Tr. at 796, 823, Dr. Arnold; Tr. at 1004, Dr. Ho; Tr. at 1003-04, Dr. Larder; TTX 71). Removing AZT would be contrary to the understanding of why that combination worked, and no good reason was given why a person skilled in the art would abandon that advantageous property. (Tr. at 1003, Dr. Larder; Tr. at 1251, Dr. Ho). Teva argues that this was just a theory, but the evidence shows that it was the best available explanation for why AZT/3TC worked where all other combinations failed.[31] Teva also points out that resensitization did not entirely explain the efficacy of the combination, but resensitization indisputably was understood to be the most significant factor. It is not disputed that 3TC and abacavir did not have a similar mutational interplay, and would not be expected to restore sensitivity to a resistant virus. There also is the issue of cross-resistance, which the Court already noted was a deterrent to combining abacavir and 3TC. For these reasons, the AZT/3TC prior art would not provide motivation for a person skilled in the art to remove AZT from the combination, and to replace it with abacavir to form the double combination.

(b) The triple combination: abacavir, 3TC, and AZT.

Lupin argues that the prior art logically led drug researchers to pursue the triple combination of abacavir, 3TC, and AZT. Lupin points out that abacavir and 3TC selected for the same mutations, and thus both would resensitize an AZT-resistant virus to AZT, making them ideal to pair with AZT. (Tr. at 764; TTX 265 at I82). Lupin further asserts that abacavir was known to show *in vitro* synergy with AZT. (LTX 1324 at S36; TTX 265 at I6, I82; Tr. at 802,

[31] Although the references indicate that scientific certainty had not been arrived regarding why the combination worked, there are multiple references explicitly tying the mutational interplay to AZT/3TC's success. Contrasted with Defendants' theory that differing analog bases would offer predictable potency and synergy, which has no supportive publications, the mutational interplay explanation is on solid ground. All of this suggests that the mutational interplay would inform persons skilled in the art when designing combinations after AZT/3TC's publicized success.

Dr. Arnold; Tr. at 1379-81, Dr. Ho). Lupin also relies heavily on a patent application of Dr. Larder, one of ViiV's experts. That application suggested combining AZT with two additional compounds, each from one of the following categories: (1) a "mutation-inducing HIV-RT inhibitor," to gain the benefit of resensitization, and (2) "other therapeutic agents." (TTX 204 at 1-2, 7; Tr. at 1379-81). 3TC is listed in the first category as one possible "mutation-inducing HIV-RT inhibitor," and carbovir is listed in the second category as one of the "other therapeutic agents." (Tr. at 778, Dr. Laurence; TTX 204 at 7). According to Lupin, the application thus specifically discloses AZT, 3TC, and carbovir. As abacavir was a carbovir analog understood to have superior bioavailability and toxicity profiles, Lupin argues a person skilled in the art would accordingly replace carbovir with abacavir in the three drug combination suggested by the Larder application, making the claimed combination obvious.

ViiV, however, rightly points out that a complete reading of the Larder application gives rise to a large number of potential combinations having many different potential benefits and challenges. While 3TC is one potential "mutation-inducing HIV-RT inhibitor" to be combined with AZT, there are also eight other drugs listed in that "inhibitor" category. (TTX 204 at 4-5). One is the NRTI known as FCT, and the seven others are NNRTIs. (TTX 204 at 2, 4-5; Tr. at 801-02, Dr. Arnold; Tr. at 750-53, Dr. Laurence).[32] The NNRTIs induce a different resensitizing mutation than 3TC (at "position 181" rather than "position 184"). (TTX 204 at 19). The application next contains the vague suggestion to add "other therapeutic agents" to "AZT and/or the mutation-inducing HIV-RT inhibitor." The "other therapeutic agents" category is exemplified by (but not limited to) a laundry list of drug classes and compounds, including protease inhibitors, interferons, and the NRTIs of ddI, 3TC (appearing again) and carbovir. (*Id.*

[32] The NNRTIs induced a different mutation than 3TC did (M181V rather than M184V) to resensitize the virus to AZT. (*Id.*). Thus, their use, unlike 3TC's use, with abacavir would not result in duplicative resensitization.

at 7). The variety of compounds in the "other therapeutic agents" category, spanning multiple classes, would leave a person skilled in the art with virtually no guidance as to which path to choose.

Although one extractable combination from the instructions is AZT, 3TC, and carbovir, there is nothing in the application that would lead a drug researcher to that specific combination to the exclusion of any other. Even combining teachings in the application with the knowledge that AZT/3TC had been proven to be the best combination, it does not follow that carbovir should be added as the third drug where those two drugs are used. It would make little sense to pluck carbovir out from the list of "other therapeutic agents" where 3TC was used as the mutation inducing inhibitor, as there were a litany of options on the list that did not share cross-resistant profiles with 3TC. In contrast, carbovir would be more predictably combined where one of the NNRTIs was used as the mutation inducing inhibitor, as overlapping resistance profiles would be avoided. The Larder application is thus not as strong a suggestion in the direction of the claimed triple combination as proffered by Lupin.

ViiV further argues that the concerns of toxicity would have taught away from the triple combination. Specifically, carbovir and AZT had been shown to display "synergistic toxicity," and thus a person skilled in the art would not seek to combine abacavir (the carbovir analog) with AZT. (PTX 451 at 146; TTX 225 at 172). NRTIs were generally expected to be toxic, as they may interfere with normal DNA processes in a similar manner as to how they inhibit the viral reverse transcription. (Tr. at 1290-91, Dr. Ho; TTX 224 at 33). Toxicity could not necessarily be predicted based on *in vitro* study or even *in vivo* animal experimentation, as ddI did not show serious toxicity when studied *in vitro* or in dogs, yet when given to humans, serious side effects emerged, including potentially lethal pancreatitis. (PTX 365 at 3949). Certain

combinations also resulted in highly toxic outcomes. For example, the combination of AZT and ddC caused "considerably more adverse reactions" due to toxicity than AZT or ddI monotherapies. (PTX 268 at PB0266; Tr. at 634, Dr. Parniak). That combination was also reported to cause "increased incidence of serious toxicity in patients with advanced disease." (PTX 432 at 4253; Tr. at 1246-47, Dr. Ho). Dr. Zingman agreed that "it was a difficult decision to know whether or not to give [patients] two toxic drugs or only one..." (Tr. at 421-22). The experts agreed that synergistic toxicity was to be avoided. (Tr. at 709, Dr. Laurence; Tr. at 1294-95, Dr. Ho; Tr. at 581, Dr. Parniak).

All of this suggests that new types of NRTI therapies retained the potential for unexpected toxicity. That potential increased the unpredictability in the field, which undercuts the argument that any particular combination would be obvious. And it is true that AZT and carbovir produced synergistic toxicity. (PTX 451 at 146; TTX 225 at 172). As discussed above, however, abacavir was successfully designed to avoid the toxicity problems of carbovir, and was understood to be a less toxic compound. (TTX 265 at I84). Further, unlike carbovir, abacavir had been progressed to clinical trials, which would increase the confidence that abacavir was safer than carbovir. (Tr. at 1374-77, Dr. Ho). Thus, concerns of abacavir's toxicity would not be the same as they were for carbovir, and the Court does not believe that carbovir's toxic synergy with AZT would be imputed to abacavir.

Lupin also argues that a person skilled in the art would be motivated to improve upon the existing AZT/3TC/ddI combination by replacing ddI with abacavir. Lupin points out that prior to March 1995, doctors had already prescribed the triple combination of AZT, 3TC, and ddI. (Tr. at 1364, Dr. Ho). Lupin posits that abacavir was a solid candidate to replace ddI in the combination, as abacavir was known to be less toxic than the very toxic ddI, yet offered greater

potency. (Tr. at 334, 362-63, Dr. Zingman; Tr. at 715, Dr. Laurence). Abacavir was structurally similar to ddI, and both selected for the M184V and L74V mutations. (Tr. at 795, Dr. Arnold; Tr. at 1041, Dr. Larder; TTX 265 at I82). Lupin heavily relies on the fact that abacavir targets the same DNA base as ddI. As discussed already, the differing analog base strategy was not shown to be established in the prior art. Thus it would not provide a motivation to make the triple combination. Lupin further does not point to any success garnered from the AZT/3TC/ddI combination that would inspire imitation. Only two abstracts discuss this combination. (LTX 1484 at 265, 268). One is a description of ongoing clinical trials that does not disclose any results. (*Id.* at 265). The second is an *in vitro* study of AZT/ddI/3TC, describing it as "the most consistent triple drug combination," but the study does not state which other combinations were less consistent. (*Id.* at 268). A single *in vitro* study claiming some degree of undefined success is not persuasive evidence of obviousness. And, as discussed, the complete cross-resistance between abacavir and 3TC provided some degree of discouragement for their combination.

(iv) Secondary considerations

The Court will consider any secondary considerations indicative of nonobviousness. "A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a 'check against hindsight bias.'" *INVISTA N. Am. S.a.r.l. v. M & G USA Corp.*, 2013 WL 3196817, *7 (D. Del. June 25, 2013). ViiV argues the secondary considerations of failures of others, long felt but unresolved needs and unexpected clinical efficacy, industry praise, skepticism, unexpected synergism, and commercial success as indicia of nonobviousness.

(a) Failures of others, unmet but long felt needs, and unexpected clinical efficacy

ViiV asserts that both the claimed combinations satisfied long felt, but unresolved needs in the marketplace for anti-HIV medicine. Defendants disagree, arguing that ViiV failed to show that the claimed combinations were superior to AZT/3TC.

Dr. Ho testified that studies showed that the abacavir/3TC combination outperformed AZT/3TC in children, and this would be surprising, because AZT/3TC was known as the gold standard of HIV treatment in March 1995. (PTX 113; PTX 122 at 738; Tr. at 1303-04, Dr. Ho). The fact that the abacavir/3TC would eliminate the resensitization benefit of AZT/3TC, yet still offered clinical efficacy, would be surprising. Dr. Ho also testified that abacavir/3TC/AZT outperformed AZT/3TC even with the M184V mutation present, and this would be surprising. (Tr. at 1307-08, Dr. Ho; PTX 257). The triple combination was also non-inferior (or comparable) to AZT/3TC plus a protease inhibitor in two separate studies. (Tr. at 1307-08, Dr. Ho; PTX 390; PTX 477). ViiV argues this would be surprising in light of the overlapping resistance profiles of abacavir and 3TC.

"In the pharmaceutical industry, the failure of others to develop a safe and effective drug often supports the nonobviousness of a drug that finally achieves success." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 923 F. Supp. 2d 602, 680 (D. Del. 2013) (citation omitted). The long-felt and unmet need inquiry is judged at the time of the filing date of the patent. *Id.* at 683. It is clear that the art of HIV treatment was littered with failures as of March 30, 1995. Only a single combination, AZT/3TC, had shown any sustained effectiveness against the virus. Despite this promising showing, that combination was still in an experimental stage, not yet FDA approved, and there was no certainty that its benefits would be sustainable in the face of a vexing disease. The question is whether the announcement of AZT/3TC's impressive clinical results a few months prior to the filing date erases the extensive history of failures in the

art. The Court does not believe that it does. Monumental efforts were being put forth in the early to mid-90s to solve the HIV public health crisis. When put to the test, nearly all of those efforts were proven to be failures. Those failures are indicia of nonobviousness in comparison with the success of the claimed combinations.

As to the actual evidence of success proffered by ViiV, it is sufficient to show that the claimed combinations are safe and effective agents at providing sustained anti-HIV therapy.[33] The success of the double combination is particularly surprising, as that combination lacked the AZT/3TC resensitization dynamic. The success of the triple combination is also surprising, as that combination added a third potentially toxic drug to the existing AZT/3TC combination, while having an overlapping cross-resistance profile with 3TC. Defendants argue that ViiV has not shown that the claimed combinations were superior to AZT/3TC, but the Court does not view that as necessary, considering that at the time of filing, the country was still in the midst of a public health crisis, and the need for more than a single effective therapy was apparent. For these reasons, the success of the claimed combinations in the midst of many failures is indicia of nonobviousness.

(b) Industry Praise

ViiV argues that the claimed combinations received industry praise, a factor which may support nonobviousness. ViiV points to the testimony of Dr. Blick, who stated that the claimed combinations gained praise for their efficacy and durability. (Tr. at 104-09). ViiV points out that they have been prescribed often, and that Trizivir was chosen to launch a highly active antiretroviral therapy ("HAART") in China. (Tr. at 1143-45, Dr. Grabowski; Tr. at 1308-09,

[33] Defendants argue that the studies cited by ViiV should be discounted, as they only show effectiveness for treatment in children, but do not explain why that effectiveness would not be correlated with effective treatment generally.

1311-12, Dr. Ho). ViiV also asserts that the single combined formulation of abacavir/3TC is currently a "preferred" regimen, in four out of six guidelines. (PTX 467; 633; PTX 637; PTX 636). Similarly, ViiV asserts that the triple combination was recommended as an alternative regimen for many years by two guidelines, and was the only triple combination to be so recommended. (PTX 487; PTX 515; PTX 532).

None of this is sufficient to create indicia of nonobviousness. ViiV has not provided any evidence of praise from other drug researchers or competitors. The testimony of Dr. Blick is unsupported by any evidence, and the fact that a drug compound is recommended by treatment guidelines or is prescribed often is more appropriately considered in the context of commercial success. All of this falls well short of showing true industry praise. *See Bayer Healthcare Pharmaceuticals, Inc. v. Watson Pharmaceuticals, Inc.*, 713 F.3d 1369, 1377 (Fed. Cir. 2013) (holding journal citations referencing efficacy studies not sufficient to show industry praise).

(c) Skepticism

ViiV argues that it has provided evidence of skepticism of others that the claimed inventions would work. ViiV points to two supposed instances of skepticism. The first is a February 1995 communication by Dr. Tisdale, a colleague of the inventors, who warned that abacavir and 3TC "clearly show some cross-resistance" and "stress[ed] that the cros[s]-resistance profile is a problem with this combination." (PTX 12 at 0745208). The second is a 2002 study, where the authors stated that, prior to the study, they were concerned that the combination might not be effective due to abacavir and 3TC's selection for the M184V mutation. (PTX 122 at 738-39).

Defendants argue that the Tisdale statement is irrelevant, as it was an untestified to hearsay statement that was not published. The Court agrees that it is not relevant, but not for

precisely these reasons. The Court is not aware of any cases where skepticism was recognized as indicia of nonobviousness when that skepticism was made by personnel internal to the company responsible for the invention. Skepticism should only be recognized as indicia of nonobviousness if it is displayed by those outside the company, as it seems conducive to the inventive process for coworkers to play the devil's advocate, that is, to probe for weaknesses and test the merits of ongoing research. Such internal dialogue has no probative value. Further, skepticism expressed in a private communication is likely less considered and less self-scrutinized than statements of skepticism intended to be published to the scientific community. For these reasons, Dr. Tisdale's statement is not indicia of nonobviousness.

As to the 2002 study, Defendants argue it is irrelevant for being published subsequent to the filing date. The Federal Circuit has stated, however, that evidence responding to attacks on validity may be obtained after the filing date of the patent. *Knoll Pharm. Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). "Relevant secondary considerations often are not manifest even until well after the issuance of a patent." *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011). This would seem to be especially true in the context of a skepticism inquiry, as it is often in the inventor's interest to maintain the secrecy of her invention as long as possible, and knowledge of the invention might only enter the public sphere (and thus become ripe for skepticism) due to an event naturally occurring after the filing date, such as the application's publication. The Court agrees with ViiV that the statement, that the risk of cross-resistance was still a concern so many years after the filing date, is relevant skepticism indicating nonobviousness. It is, however, only a single statement, and therefore is an insignificant factor in the final weighing of the evidence.

(d) Unexpected synergism

(i) Was synergism expected?

Defendants argue that the synergism of the claimed combinations was to be expected, as abacavir, 3TC, and AZT all operate as analogs of different DNA bases, and all of the clearly synergistic combinations in the prior art also involved NRTIs of different analog bases. As discussed *supra*, however, the only evidence that synergism was positively understood to result from these types of combinations is unsupported expert testimony. It is beyond doubt that experts were aware of the nature of NRTIs as analogs of a particular DNA base, and it is also true that experts were aware of combinations producing synergy. There is no evidence, however, that the field put two and two together to deduce that synergism was actually caused by (or even correlated with) combinations assembled from different analogs. There is little doubt that, were such a relationship established in the field, it would have been reported in some study, publication, or textbook in the prior art.

The only support Defendants can point to is Dr. Ho's testimony that drug researchers would avoid using nucleoside analogs based on the same DNA building block. Knowing it is best to avoid combining drugs based on the same block out of an apparent desire to avoid antagonism is not equivalent to reasonably predicting that combining drugs based on different blocks will result in synergism. For these reasons, Defendants do not show that "POSAs understood that complementary NRTIs exhibited synergistic effects[.]" (D.I. 205 at 28).

(ii) Synergy evidence

The next question is whether ViiV factually proved the synergistic effects of the claimed double and triple combinations. The parties dispute the trustworthiness of the data relied upon by ViiV's synergism expert, Dr. Greco, for his opinion that synergy was shown for both combinations. Dr. Greco received the data from Mr. Hazen, the Glaxo employee who conducted

the experiments. (Tr. at 1098-99, Dr. Greco). Mr. Hazen admitted that the data sets were affected by control problems. (Tr. at 1072-72). Nevertheless, Dr. Greco relied on the data for his model, finding the drug combinations synergistic. (Tr. at 1088-90, 1107-08, 1108-09; PTX 567; PTX 569; PTX 576; PTX 579).

Defendants argue that problems with the controls of Mr. Hazen's experiment make Professor Greco's opinion unreliable. The problem involved the wells of uninfected and untreated human cells. (Tr. at 1072-74, Mr. Hazen). As the control group, the uninfected cells were intended to provide the theoretical upper bound for the measurement of living human cells in comparison with the infected cells. (Tr. at 1452, Prof. Makuch). The results of the test, however, showed that wells of infected cells plus AZT actually had a higher number of living cells than the control group, counterintuitively suggesting that HIV infection increased rather than decreased human cell production. (Tr. at 1452-53, Prof. Makuch). Professor Makuch, Defendants' expert, testified that it was much more difficult to measure the effect of the drugs absent the control group for comparison. (Tr. at 1454-55). He also noted that certain wells containing lesser dosages of the drug resulted in greater suppression of replication than wells with greater dosages, when the opposite would be expected. (Tr. at 1454).

ViiV argues that issues with the control group do not necessarily imply issues with the infected cells. Dr. Greco testified that he was able to rely on the infected cells treated with drugs at high concentrations in place of the control because they characterized the "upper asymptote very, very well." (Tr. at 1102-03). Mr. Hazen found the data was reliable because the infected cells were treated differently than the uninfected cells, and the calculations from the infected cells produced a smooth, S-shaped curve. (Tr. at 1058-60).

Professor Makuch explained that Dr. Greco's attempt to salvage the validity of the experiment was problematic because ignoring the control group violated the original design of the experiment, which included the control group to provide a baseline for data comparison. (Tr. at 1455). He also explained that problems with the control group put the values of all wells in the experiment in doubt. (Tr. at 1455-56). Professor Makuch opined that the proper way to remedy the problem was to replicate the experiment to provide a check on the data obtained, rather than to ignore the control group. (Tr. at 1456). Professor Makuch also testified that wells at columns five through nine were concerning. (Tr. at 1457). Those columns represented serial dilutions of the drug with other variables constant, yet had a flat dose response, *i.e.*, the values did not vary despite differences in drug potency. (Tr. at 1457). He further noted that even if Hazen's experiment had been conducted perfectly, it was only a single experiment, and further experimentation should have been performed to assess validity and account for variability. (Tr. at 1457).

The Court credits Prof. Makuch's testimony. The control group was there for a reason, and simply ignoring it is not consistent with the original intent of the experiment. Further, anomalies in the control group not only required the removal of the baseline, but also place a degree of doubt into the data accumulated from the infected wells, even if they were "treated differently" than the uninfected cells. That doubt is enlarged by counterintuitive findings that certain wells with lesser drug concentration showed greater viral replication than wells with greater drug concentration. One of these problems in isolation might not necessarily undermine Dr. Greco's conclusions relying on the Hazen data, but in combination they are troubling enough so that I cannot conclude his opinion is based on reliable data. I therefore do not credit it.

The Hazen data is not the only source of alleged synergy proffered by ViiV. ViiV also provided testimony from Martha St. Clair, one of the '191 Patent's inventors. Defendants argue that this evidence is also not reliable. Ms. St. Clair testified that she generated results showing synergy, relying on her lab notebooks. (Tr. at 918-920, 934-35, 959; PTX 12; PTX 13). She also admitted that she did not include one set of data indicating antagonism, as that set involved a very high concentration of 3TC, and drugs at high levels sometimes do not behave in an appropriate fashion. (Tr. at 961-63). Defendants argue that Ms. St. Clair's exclusion of results indicating antagonism proves she cherry-picked from data sets. The Court does not agree that Ms. St. Clair's exclusion of a single data set showing antagonism from the totality of her results renders those results untrustworthy. If Defendants put forth evidence that the claimed combinations were in fact antagonistic, rather than "not synergistic," the exclusion of those results might put the St. Clair data into serious question. There does not seem to be a genuine dispute, however, that the drug combinations are not antagonistic.[34] It is thus reasonable to conclude that the data excluded by Ms. St. Clair was in fact not reflective of the actual drug activity. The only other criticism Defendants have of the St. Clair data is that two points of data were slightly misplotted. (Tr. at 956-61, Ms. St. Clair). Ms. St. Clair, however, testified that even with accurate plotting of those two points, the data still showed synergy, and that testimony was not discredited. Ms. St. Clair also testified as to the synergy of the two drug combination disclosed in the Daluge 1997 article that she co-authored, but that article only contains an isobologram, without the underlying data points, so it is less persuasive evidence. (PTX 296; Tr. at 936-39). Nevertheless, the St. Clair data is thus sufficient for a showing of the *in vitro* synergy of the claimed combinations.

[34] If Lupin and Teva actually believed the claimed combinations resulted in antagonism, they would likely not seek to bring generic forms of those drugs to market.

Defendants do point to some evidence suggesting that the claimed combinations did not show synergy. Mr. Hazen authored a report to his supervisors, which was forwarded to the FDA, suggesting that the ABC and 3TC combination was additive rather than synergistic. (TTX 61 at 0046905; Tr. at 1079, Mr. Hazen). Dr. Tisdale also stated that ABC and 3TC was an additive combination in an internal communication to Ms. St. Clair, while allowing that abacavir, 3TC, and AZT showed some synergy. (PTX 12 at 745208; Tr. at 968-70, Ms. St. Clair). Defendants, however, point to no actual data supporting any argument that the combinations were merely additive. Absent such a showing, the Court will rely on Ms. St. Clair's testimony and her lab notebooks as accurate.

That being said, the only evidence proffered by ViiV related to *in vitro* synergy. The fact that the claimed combinations show synergism *in vitro* is not enough to prove unexpected results. In fact, many combinations had been shown to be synergistic *in vitro*, as explained throughout the opinion (*E.g., supra*, pg. 26, 27), and ViiV repeatedly criticized those results as not sufficient to conclude that combination therapy would provide clinical results. A showing of synergy *in vitro*, without correlative *in vivo* success, is not enough. Although ViiV has shown unexpected clinical efficacy as explained above, the evidence of synergism *in vitro* is not evidence of unexpected results.

(e) Commercial success

The parties dispute whether Epzicom and Trizivir, the commercial embodiments of the `191 Patent, have been proven to be commercial successes. "Commercial success is relevant because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). "Thus, the law

deems evidence of (1) commercial success, and (2) some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention, probative of whether an invention was non-obvious." *Id.*

The Court must first define the relevant market. ViiV argues that the relevant market is limited to drug products in the NRTI class. Defendants argue that the relevant market is all classes of anti-HIV drugs. Dr. Grabowski, ViiV's expert, testified that the market is limited to NRTIs, rather than the anti-HIV drug market as a whole, because that is consistent with how the drugs are prescribed for treatment. (Tr. at 1146). Specifically, Epzicom and Trizivir are prescribed as the "backbone" of HAART therapy, and are then combined with another drug from a different class, either a PI or an NNRTI. (Tr. at 1146-47). According to Dr. Grabowski, drugs from other classes complement NRTIs and do not take sales away from NRTIs; and the focus for the commercial success analysis should thus center on the market for the NRTI "backbone" of HAART therapy. (Tr. at 1146-47). Mr. McSorley, Defendants' expert on obviousness, disagreed, pointing out that ViiV's internal documents defined the market as including products in other drug classes, including PIs. (Tr. at 1420; LTX 1224). Defendants further argue that because patients can take more than one NRTI at a time, and also because NRTIs themselves can be complementary to each other, it makes no sense to define the NRTI market as separate from other drug classes. (D.I. 221 at 30).

The Court agrees with ViiV that the relevant market for Epzicom and Trizivir is the NRTI market. Dr. Grabowski's testimony as to how Epzicom's and Trizivir's use in treatment drives sales and determines the market is persuasive. There are two general components of HAART therapy: (1) an NRTI "backbone" matched with (2) a drug of another class.[35] It would

[35] ViiV's evidence of what HAART therapy consists of is unchallenged by Defendants. Defendants further do not put forth evidence that a different type of HIV therapy drives the market.

make no sense for a doctor to consider prescribing a PI or an NNRTI for the "backbone" of HAART therapy, as the "backbone" itself must be comprised of NRTIs. The realities of treatment thus dictate that PIs and NNRTIs generally do not compete with NRTIs for sales. While ViiV's internal "launchplan" showed an intention for the commercial embodiments to compete with all anti-HIV drug classes, Mr. McSorley's contention that ViiV's launchplan determines the market is not persuasive. ViiV's internal aspirations for market dominance are not evidence of how the drugs are prescribed in practice, and are thus less probative when determining the relevant market.

Defendants further argue that it illogical to say that because NRTIs are complementary to other classes of drugs, they are in a different market from those drugs, where the evidence shows that NRTIs themselves can be complementary to each other. It is true that NRTIs in one sense may be described as complementary to one another, *i.e.*, the much discussed AZT and 3TC combination. They complement one another, however, in performing the same anti-HIV function, *i.e.*, acting as chain terminating nucleosides. The other anti-HIV drug classes attack viral replication in a fundamentally distinct way. For example, a PI disrupts replication by selectively inhibiting the protease enzyme, which interferes with the virus's cleaving process. The mechanism is completely different, and this explains why doctors prescribe NRTIs and PIs together as "complementary" drugs, and would not consider one as a substitute for another, even if NRTIs can also be labeled as "complementary" to each other in a different sense. The market for Epzicom and Trizivir is the NRTI market.

The next question is whether Epzicom and Trizivir garnered a substantial quantity of the NRTI market. Over 2.5 million prescriptions have been filled for both drugs since their introduction to the market. (PTX 77; Tr. at 1145). The two drugs were rapidly accepted in the

market place, with Epzicom garnering over 200,000 prescriptions in its first year, and Trizivir garnering almost 400,000 prescriptions by year three on the market. (Tr. at 1143-44). Dollar sales of Epzicom and Trizivir are over $3 billion each, with the cumulative profitability of both drugs over $1.6 and $1.56 billion, respectively. (PTX 76; PTX 78; PTX 83). To argue that they are not commercial successes, Defendants point to the fact that other NRTI products such as Truvada and Combivir have outperformed Epzicom and Trizivir. The fact that a commercial embodiment is not the most popular product on the market, however, does not dictate that the embodiment is not a commercial success. Although Trizivir and Epzicom did not capture the greatest share of the market, they are solidly in the top half of NRTIs through their sales history. (PTX 76; PTX 78; PTX 83). Epzicom has consistently outperformed the majority of other NRTIs on the market, and Trizivir did as well during the peak years of its life-cycle. Their market shares are sufficient to find them reasonably successful compared with the competition.

ViiV must not only show that Trizivir and Epzicom are successful drugs, but that there is a close nexus between that success and the claims of the `191 Patent. *Transocean*, 699 F.3d at 1350. If the success was due to factors other than the benefits intrinsic to the invention, such as marketing or, relevant here, the existence of blocking patents, the nexus may not exist. *See Teva*, 395 F.3d at 1364. There is little dispute that Trizivir and Epzicom are the commercial embodiments of the `191 Patent's claims.[36] Trizivir and Epzicom were "tier two formularies" 76 and 77 percent of the time, meaning that they are designated "preferred drugs" by insurers.[37] The designations supports the finding that the products are successful due to their therapeutic qualities. (Tr. at 1162, Dr. Grabowski).

[36] Lupin says there was no testimony that Trizivir contains abacavir free base. (D.I. 221, p. 17). Dr. Ho did testify that Trizivir was "covered by the asserted claims of the `191 patent." (Tr. 1324).

[37] Tier 1 drugs are generally reserved for generic drugs. (Tr. at 1160, Dr. Grabowski). Third tier drugs are non-preferred and have higher co-pays than preferred drugs. (Tr. at 1160, Dr. Grabowski).

Key to the nexus question is whether the commercial success was due to the beneficial characteristics of the invention, or can be attributed to the existence of blocking patents.[38] Defendants main argument is that the existence of "blocking patents," owned or controlled by the same patentee, prevented competitors from developing the invention earlier in response to "market forces," citing *Teva*, 395 F.3d at 1376-77. The claimed combinations were developed by Burroughs Wellcome, who also invented AZT and abacavir individually and held patents for those two drugs. (Tr. at 1165, Dr. Grabowski). The rights to commercialize 3TC were licensed to Glaxo from a company known as Biochemical Pharma. (Tr. at 1414-15, Mr. McSorely). Glaxo entered into a letter of intent with Burroughs Wellcome, licensing some of the 3TC patent rights in March 1994. (Tr. at 1414-15, Mr. McSorely).

Mr. McSorley's opinion that the patents effectively halted any other company from pursuing the claimed combinations relied on the fact that "other researchers would not have been able to conduct such research to begin with because of the patents[.]" (Tr. at 1418). It is true that Burroughs Wellcome had the right to exclude others from working on all three drug compounds as of the effective filing date. Burroughs Wellcome only had the right of exclusivity for a short period of time, however. The rights to market 3TC were gained in March 1994, and Martha St. Clair performed her tests showing the synergism of the double and triple combinations in June 1994. This is not a situation where a patentee was able to "block" others from attempting to make the claimed inventions for many years- they were formulated a matter of months into Burroughs Wellcome's exclusivity period. It is also not disputed that researchers frequently shared compounds with other companies in the HIV field to help create new HIV therapies. (Tr. at 881-83, Ms. St. Clair; Tr. at 1164-66, Dr. Grabowski; Tr. at 1198, Dr. Hausman). Although

[38] There is no evidence that marketing or promotion drove the sales of either drug. (Tr. at 1162-64, Dr. Grabowski).

Burroughs Wellcome had exclusive rights to use all three compounds as of the effective filing date, it had only obtained the right to 3TC a relatively short time prior. Thus, the inference that the commercial success was due to "blocking patents" is lessened.

Thus, this is not a situation where the commercial success of the drugs can be completely attributed to blocking patents. The Court finds that the commercial success of Epzicom and Trizivir is indicia of nonobviousness, although not as strong of an indication as would exist in the absence of the patent rights that Burroughs Wellcome held.

(B) LEGAL DISCUSSION AND CONCLUSIONS OF LAW

Section 103 bars patentability unless "the improvement is more than the predictable use of prior art elements according to their established functions." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 401 (2007). A patent claim is obvious "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). To prove a case of obviousness, Defendants must show that a person skilled in the art would be motivated to combine the claimed combinations with a reasonable expectation of success. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). Evidence of obviousness, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and that skilled artisans would have had a reason to select the route that produced the claimed invention. *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012). Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

Defendants did not meet their burden. There was very little about anti-HIV therapy that could be described as predictable as of March 1995, and the history of failure in the field offered persons skilled in the art little reason to expect that any particular combination would work. Concerns of toxicity, potency, cross-resistance profiles, HIV's ability to mutate swiftly, a large universe of potential compounds and drug classes, and rapidly dying patients in the midst of a public health crisis made assembling an effective drug combination extremely challenging. In the months preceding the filing of the `191 Patent, the state of the art was extremely fluid. News of disheartening setbacks were followed by important advances in what was a fast moving field. Monotherapy options had been exhausted, and although the field generally accepted the premise that combination therapy was the future of HIV treatment, no clear cut clinical benefit had been shown prior to the reports of AZT/3TC's success in December 1994. These results were exciting precisely because of the pervasive failure encountered in the field, as years of testing antiviral agents either alone or in combination showed that while the drugs would initially reduce a patient's viral load, it would return to baseline levels after six months of treatment. The promise of AZT/3TC in no way erased the reality that combining anti-HIV drugs was a highly uncertain endeavor, and there was little expectation that any particular combination would work.

Defendants argue that AZT/3TC provided a reference point that made the claimed combinations of the `191 Patent obvious, but as Defendants point out, the molecular mechanisms underlying why the AZT/3TC combination was successful were not entirely understood. This observation cuts against finding the claimed combinations obvious, as the less understanding that exists in a field, the less the likelihood that any particular new therapy in that field is obvious. A finding of obviousness seems incompatible in a field where (1) almost all therapies failed to provide sustained results and (2) the sole success story was not completely understood. The

reality that combination therapy was still quite confusing for persons skilled in the art is confirmed by the words of the February 1995 issue of *AIDS Weekly*, which stated that AZT/3TC "*may* lead to rational strategies for combination therapy *instead* of random choices from a wide array of drugs." (TTX 71 at 2) (italics added). Researchers felt their efforts in combination therapy were beset by "random choices from a wide array of drugs." The hope was that "rational strategies" were forthcoming, but the field was not quite there yet. This was the state of the art less than six weeks prior to the effective filing date of the `191 Patent, and months after Martha St. Clair did her first testing and compiled results of the claimed combinations.

The state of the art as described in the *Aids Weekly* report is inconsistent with the law underlying Defendants' "obvious to try" theory. The "obvious to try" standard follows:

> When there is a design need and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR, 550 U.S. at 421. Where researchers have to resort to a wide array of options and are required to select drugs randomly, it cannot be said that "a finite number of identified, predictable solutions" existed. Defendants' "differing DNA bases" theory cannot serve to narrow the options or to make the efficacy of the claimed combinations predictable, as it was not supported in the art. Abacavir's status as a strong candidate for combination therapy does not convert the combination selection process into a reasonably predictable endeavor. Further, the argument that the AZT/3TC combination made the double combination obvious is contradicted by the then-existing best explanation for the AZT/3TC combination's success, *i.e.*, the special mutational interplay resensitizing the virus to AZT. As to the claimed triple combination, while it retained the special AZT/3TC dynamic, no three-drug NRTI combination had shown sustained clinical efficacy as of the filing date. In that sense, the abacavir, 3TC, and AZT was a first of its

kind combination. The inherent risk of toxicity associated with adding a third NRTI to AZT/3TC lowered the expectation that the three drug combination would be successful, even considering the fact that abacavir and 3TC were second generation NRTIs associated with less toxicity than first generation NRTIs. The overlapping drug profiles of abacavir and 3TC also taught away from their combination. The secondary considerations also suggest that nonobviousness of the claimed combinations. Both Epzicom and Trizivir must be regarded as commercial successes, and both succeeded in providing clinically effective treatment in a field where many others had failed, despite monumental efforts to succeed. All of these considerations results in the conclusion that the Defendants have not proved the obviousness of the claimed inventions by clear and convincing evidence.

Novo Nordisk A/S v. Caraco Pharm. Laboratories, Ltd., 719 F.3d 1346 (Fed. Cir. 2013), cited by Defendants, is not persuasive otherwise. In *Novo Nordisk*, the Federal Circuit upheld the district court's finding that a two-drug combination treatment for Type II diabetes was obvious. *Id.* at 1351. The combined drugs were metformin, a well-known and successful drug used to improve insulin sensitivity, and repaglinide, a new sulfonylurea-class insulin secretagogue that worked to stimulate insulin release from pancreatic beta cells. *Id.* at 1349. It was not disputed that it was well-known in the art that two drugs having different mechanisms for attacking diabetes were more effective than one, and drugs were often tested in combination therapy after demonstrating effectiveness in monotherapy. *Id.* at 1351. Combinations of insulin sensitizers and insulin secretagogues were common at the time, and the patentee's failure to prove that the synergy shown was unexpected doomed the claims as obvious. *Id.* at 1349, 1355.

There are some superficial similarities between *Novo Nordisk* and the case at hand. Both involve combination therapies and a failure to show unexpected synergistic effects. The

commonality ends there. In *Novo Nordisk*, the patentee's showing of synergistic effects was not surprising, as the district court found that the combined drug classes had been used together for more than 30 years. *Novo Nordisk A/S v. Caraco Pharm. Laboratories, Ltd.*, 775 F. Supp. 2d 985, 1003 (E.D. Mich. 2011). The drug classes had a well-known history of being used together for beneficial results. *See Novo Nordisk*, 719 F.3d at 1355. That history went a long way to make combining metformin and repaglinide a predictable endeavor. *See id.* The first effective HIV combination therapy, in contrast, was only announced a few months before the `191 Patent's filing date. The degree of understanding in the field of the *Novo Nordisk* combination was literally a generation ahead of the understanding in the anti-HIV field. Further, although ViiV did not establish unexpected synergy, ViiV did show unexpected clinical efficacy, and any sustained clinical efficacy was seen as a breakthrough as of March 1995. Another significant difference is that the drugs in *Novo Nordisk* were known to be generally effective individually for diabetes treatment, whereas the NRTIs of the claimed combinations all failed to treat HIV infection as monotherapy. It takes less of a leap of faith to conclude that drugs that provide effective treatment individually would work well in tandem, especially where they have different mechanisms of action, as the drugs of *Novo Nordisk* do. It takes a much larger leap to predict that monotherapy failures will turn the corner to effectiveness when used together. Finally, there is no indication that the field of diabetes treatment was littered with the challenges facing persons skilled in the art seeking to treat HIV, and there apparently were no other secondary considerations suggesting nonobviousness in *Novo Nordisk*. For these reasons, *Novo Nordisk* does not compel the Court to find the claimed combinations obvious.

Defendants have not proven the obviousness of any of the claims of the `191 Patent by clear and convincing evidence.

III. ENABLEMENT

A patent's specification must enable the claimed invention. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). For a patent claim to be enabled, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . ." 35 U.S.C. § 112. Furthermore, "[t]he scope of enablement . . . is that which is disclosed in the specification plus the scope of what would be known to one of ordinary skill in the art without undue experimentation." *Nat'l Recovery Technologies, Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1196 (Fed. Cir. 1999).

Defendant Lupin argues that the method claims are invalid as they encompass inoperable embodiments. Specifically, Lupin contends that as the full scope of the method claim recites "an infected animal" and as the specification only enables the method claims for humans the claims cannot be enabled.[39] (D.I. 202 at 33-34). ViiV responds that the claims are in fact limited to "infected animals" which "is much narrower than 'all animals'" and thus the claims "do not include any inoperative embodiments." (D.I. 212 at 57).

(A) FINDINGS OF FACT

The only animals that are able to contract HIV are humans and "potentially chimpanzees." (Tr. 731).

(B) LEGAL DISCUSSION AND CONCLUSIONS OF LAW

Whether a patent claim is enabled is a question of law based upon the underlying facts of the case. *Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). Here,

[39] Lupin does not contest dependent claims 30 and 39 of the `191 Patent on these grounds as the claims are limited to treating humans. (D.I. 202 at 33).

the burden of proof must be carried by the Defendants, and must be proven by clear and convincing evidence. *Cephalon, Inc. v. Watson Pharm., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013). "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue experimentation." *Id.*

Here, the patent explicitly refers to an infected animal, not simply an animal. `161 Col. 12: 32-35.[40] Thus, while Lupin's arguments may have had some appeal if the patent claims did not limit the term animal, here the patent claims explicitly limit themselves to animals that are infected. Lupin claims that the `161 patent's specification defines the term "infected animal" to include "any mammal and humans." (D.I. 221 at 32). The Court disagrees. The Court finds that the while the patent discusses that, "The components of the combination which may be referred to as active ingredients may be administered for therapy to an animal e.g. a mammal including a human in a conventional manner," `161 Col. 5: 4-7, this section does not act to define the term "infected animal" only that the components can be administered to an animal. Therefore, as Lupin's contentions rely upon the assumption that the patent must enable the treatment of at least all mammals, not simply infected animals, Lupin has failed to bring forth sufficient evidence to prove that the `161 Patent is not sufficiently enabled for a POSA to utilize the patent without undue experimentation.

IV. UTILITY

Patents may only be issued for inventions that are "useful to some extent and in certain applications . . . ." *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180 (Fed. Cir. 1991). However, "[a]n invention need not be the best or the only way to accomplish a certain result, and it need

[40] Claim 1of the `161 patent, which is representative, states in part "A method for the treatment or prevention of the symptoms or effects of an HIV infection in an infected animal which comprises treating said animal with a therapeutically effective amount of a combination comprising . . . ." `161 Col. 12: 32-35.

only be useful to some extent and in certain applications. . . . The fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Id.* (internal brackets, citations, and quotation marks omitted).

Here, Lupin argues that because the patentee "provide[d] no human or animal data regarding the three-drug combination's safety, efficacy, toxicity, etc.," the patent specification discloses no "credible utility." (D.I. 202 at 31-32). In turn, the Plaintiff argues that "credible utility" was disclosed as "a POSA would believe that the claimed combinations would have 'therapeutic utility'" considering that the `191 Patent describes the claimed combinations and "the `191 Patent includes *in vitro* data on the ability of abacavir, 3TC, and AZT alone and in combination to inhibit HIV replication at 'trough' drug concentrations determined from human clinical studies." (D.I. 212 at 53-54).

For a Court to find that a patent claim is not useful, "the claimed device must be totally incapable of achieving a useful result." *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed. Cir. 1992). This is ultimately a question of fact. *Id.* While the parties discuss *in vitro* versus *in vivo* studies, "Testing for the full safety and effectiveness . . . is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office . . . proceedings." *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994).

Utility is proven where there is evidence of the patent claim's commercial success. *Raytheon Co. v. Roper Corp.*, 724 F.2d 951, 959 (Fed. Cir. 1983); *see also Temco Elec. Motor Co. v. Apco Mfg. Co.*, 275 U.S. 319, 328 (1928) (finding that commercial success demonstrated that the patent claim was useful). As in *Raytheon*, the Court's finding *supra* that the "inventions set forth in the claims . . . have on their merits been met with commercial success," 724 F.2d

951, 959 (Fed. Cir. 1983), further supports the Court's finding that the `191 patent is not invalid for lack of utility.

Additionally, "Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." *In re Brana*, 51 F.3d 1560, 1568 (Fed. Cir. 1995). Here, the `191 Patent specification itself includes *in vitro* data on the ability of abacavir, 3TC, and AZT to inhibit HIV replication. `161 Col. 11:65 - 12:25. As was discussed by Martha St. Clair, the assays were conducted in MT-4 cells, which allowed for a robust assay. (Tr. at 901). The presence of this assay in the patent, in combination with the knowledge of a POSA, is sufficient to establish a "credible" utility for the `191 Patent. Lupin's argument that because the patent did not include *in vivo* test results the patent lacked utility, is unpersuasive and runs counter to the Federal Circuit's holding in *In re Brana.*

The Court finds that Lupin has not shown by clear and convincing evidence that any of the claims of the `191 Patent are invalid due to a failure to show utility.

V. STANDING

Standing in a patent infringement suit is governed by Federal Circuit case law. *Morrow v. Microsoft Corp.*, 499 F.3d 1332, 1337 (Fed. Cir. 2007). Whether a party has standing is based upon "whether the constitutional or statutory provision on which the claim rests properly can be understood as granting persons in the plaintiff's position a right to judicial relief." *Id.* at 1339 (quoting *Warth v. Seldin*, 422 U.S. 490, 500 (1975)). The Federal Circuit has determined that there are three types of plaintiffs that may be encountered when determining whether there is standing: "those that can sue in their own name; those that can sue as long as the patent owner is

joined in the suit; and those that cannot even participate as a party to an infringement suit." *Id.* "When a party holds all rights or all substantial rights, it alone has standing to sue for infringement. . . ," and would thus fall under the first category. *Id.* at 1340. "Parties that hold the exclusionary rights are often identified as exclusive licensees, because the grant of an exclusive license to make, use, or sell the patented invention carries with it the right to prevent others from practicing the invention. However, these exclusionary rights 'must be enforced through or in the name of the owner of the patent,' and the patentee who transferred these exclusionary interests is usually joined to satisfy prudential standing concerns." *Id.* (footnote omitted). Finally, "[t]he third category of plaintiffs includes those that hold less than all substantial rights to the patent and lack exclusionary rights under the patent statutes to meet the injury in fact requirement." *Id.*

Here, the Defendants contend that while ViiV UK "was the sole owner of the `191 Patent at the time suit was filed and has standing to sue on that basis," ViiV Co. "lacks standing and must be dismissed . . . ." (D.I. 208 at 9). Specifically, the Defendants argue that the Cost Sharing Agreement ("the Agreement") between ViiV Co. and ViiV UK is not sufficient to grant ViiV Co. an exclusive license. The Plaintiffs rebut by arguing that the aforementioned agreement is sufficient to create an exclusive license. The Court agrees.

The Court finds that the Agreement between ViiV Co. and ViiV UK granted ViiV Co. an exclusive license. Here the Agreement is subject to Pennsylvania law. (D.I. 206-1 at 63). In Pennsylvania,

> [t]he law of contracts requires contractual terms that are clear and unambiguous to be given effect without reference to matters outside the contract. Further, a contract must be construed as a whole and the parties' intentions must be ascertained from the entire instrument; effect must be given to each part of a contract. A contract is deemed "ambiguous if it is reasonably susceptible of different constructions and capable of being understood in more than one sense. Therefore, a contract will be

> deemed unambiguous if reasonable persons could not differ as to the contract's interpretation.

Purdy v. Purdy, 715 A.2d 473, 475 (Pa. Super. Ct. 1998) (internal citations and quotation marks omitted).

Two sections of the agreement are relevant to the determination of whether there is an exclusive license: (1) "Rights of Parties in ViiV Cost Shared Intangibles" and (2) "Definitions." First, the section entitled "Rights of Parties in ViiV Cost Shared Intangibles" states in part:

> Each Party or its designated Affiliates shall be entitled to exclusive ownership including the exclusive right to exploit within their respective geographic markets of all items of ViiV Cost Shared Intangibles developed pursuant to this Agreement, regardless of which Party owns legal title to the ViiV Cost Shared Intangibles. The geographic market of ViiV Co and its Affiliates shall be the United States, and that of ViiV Ltd and its Affiliates shall be the rest of the world.

(D.I. 206-1 at 59). Second, the Definition section of the same Agreement, states in part:

> "ViiV Cost Shared Intangibles" shall mean any patents, patent applications, new drug applications, product license applications, inventions, formulae, specifications, protocols, processes, designs, patterns, trade secrets, know-how, . . . that relate to ViiV Cost Shared Products (a) that are generated, developed, or first reduced to practice by or on behalf of, either or both of the Parties or their Affiliates pursuant to this Agreement, or (b) that relate to ViiV Cost Shared Products and are acquired by transfer by, or on behalf of, either or both of the Parties, but only if such acquisition results in substantial direct benefits to both Parties.

(D.I. 206-1 at 55 (emphasis removed)). The Court finds that it is clear from the four corners of the Agreement that the `161 patent is a "ViiV Cost Shared Intangible" and thus is subject to the "Rights of Parties" clause of the Agreement. The `161 patent meets part (b) of the definition of "ViiV Cost Shared Intangibles." First, the patent was "acquired by transfer by, or on behalf of, either of the parties."[41] And second, the acquisition resulted in "substantial direct benefits to both Parties" as required by the Agreement. While the Defendants claim that there has not been a showing that both ViiV UK and ViiV Co. received a substantial direct benefit, the Court

[41] The `161 patent was acquired in April 2011, after the Agreement was signed. (D.I. 208 at 12).

disagrees. Epzicom and Trizivir, the commercial embodiments of the '191 Patent, have a cumulative profitability of over 1.5 billion and 1.56 billion dollars respectively. (*See* the Court's findings *supra*). Furthermore, as ViiV Co. is a wholly-owned subsidiary of ViiV UK, (D.I. 206-1 at 47-48), its profits provide substantial direct benefits to ViiV UK. These two facts alone are sufficient to find that there is a "substantial direct benefit" to both ViiV UK and ViiV Co.[42]

For all these reasons, the Court finds that ViiV Co. has standing.

VI. CONCLUSION

The Plaintiffs have failed to prove that Lupin's generic product infringes the '191 Patent. The Defendants have not proven by clear and convincing evidence that any of the asserted claims of the '161 Patent are invalid.

The Plaintiffs should submit an agreed upon form of final judgment within two weeks.

[42] The Court finds that even if the contract was ambiguous as written, Mr. William Collier's unrebutted declaration that ViiV UK owned the '191 patent and that ViiV Co. was the exclusive licensee, provides an alternative basis for ViiV Co. to have standing in this case. (D.I. 222-3 at 5, 6).